PERIPARTUM CARDIOMYOPATHY AND THE POSSIBLE ROLE FOR AIR POLLUTION

By

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Abstract

Peripartum Cardiomyopathy (PPCM) is a rare and potentially life-threatening form of dilated cardiomyopathy that strikes previously healthy women in the last month of pregnancy or up to 5 months after delivery and can have a profound effect on the young women as well as their families. The cause of PPCM is not fully understood, but is most likely multifactorial and driven by a vasculotoxic environment caused by late pregnancy hormones. Factors such as oxidative stress, inflammation, infection, and anti-angiogenic molecules may also increase susceptibility to PPCM. Based on the known associations between $PM_{2.5}$ exposure and cardiovascular disease as well as potential mechanistic overlaps in pathophysiology including oxidative stress and inflammation, exposure to $PM_{2.5}$ during pregnancy and post-delivery may increase the risk of developing PPCM.

For this thesis project we created a new cohort from the Rochester Epidemiology Project (REP) because the REP provides a unique opportunity to study relationships between environmental exposures, such as $PM_{2.5,}$ and disease outcomes including PPCM at a population level with increased generalizability and reduced misclassification by using medical record review to confirm diagnosis. A case control study was designed to examine whether exposure to $PM_{2.5}$ during or after pregnancy increases susceptibility to PPCM.

The results from the case study suggest that in this rural area traffic-based surrogates for $PM_{2.5}$ are not good measures of exposure and $PM_{2.5}$ air monitoring would be the most accurate exposure metric. However, we found that the current level of monitoring in rural areas is not sufficient to assess relationships between $PM_{2.5}$ exposure and potential resulting health effects such as PPCM. Increased funding to develop and implement a

monitoring system based on scientific and not just compliance measurement needs would allow the US EPA to increase protection of human health from air pollution including $PM_{2.5}$ for pregnant women. Without these changes the US EPA may fail to meet its duty to protect human health with an adequate margin of safety as is required by the Clean Air Act.

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This dissertation is dedicated to my father, the first Dr. Douglass. Thank you Papi for getting me started and encouraging me along no matter what. I miss you and I am sorry we could not be Dr. Douglass' together.

Stephen A. Douglass
(1940 – 2020)

AND

Liam Walker – my partner – because you said I had to dedicate my dissertation to you if I ever finished it. Thanks for not letting me give up and always supporting me.

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Abbreviations

16Kd, 16-kDa form of prolactin

ACE-I, angiotensin-converting enzyme-inhibitor

AHA, American Heart Association

Air Quality System (AQS)

Air Quality System Monitoring Network, EPA OAR OAQPS

Annual Average Daily Traffic (AADT)

ARB, angiotensin receptor blockers

ARNI, angiotensin receptor neprilysin inhibitor

BMI, body mass index

BNP, brain natriuretic peptide

BPM, beats per minute

CVD, cardiovascular disease

CathD, cathepsin D

CCS, Canadian Cardiovascular Society

CAA, Clean Air Act

CAD, coronary artery disease

CRP, C-reactive protein

DCM, dilated cardiomyopathy

ECG, electrocardiogram

ECHO, echocardiogram

EF, ejection fraction

Environmental Law Reporter (ELR)

Fas/Apo1, Fas/apoptosis antigen 1

GBS, group B strep

GDMT, guideline directed medical therapy

GED, general educational development or general education diploma

HDP, hypertensive disorders of pregnancy or hypertensive diseases of pregnancy

HEI, Health Effects Institute

HFA ESC WG PPCM, Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy

HFrEF, heart failure with reduced ejection fraction

HICDA, Hospital International Classification of Disease Adaptation

HT, hypertension

ICD, *International Classification of Diseases*

IL-1β, interleukin 1 beta

IL-6, interleukin 6

IFN-γ, interferon gamma

IPAC, Investigations of Pregnancy Associated Cardiomyopathy

ISA for PM, Integrated Science Assessment for Particulate Matter

IQR, interquartile range

kDa, kilodalton

LA, left atrial

LDL, low-density lipoprotein

LV, left ventricle/ventricular

LVAD, left ventricular assist device

LVEDD, left ventricular end diastolic diameter

LVEF, left ventricular ejection fraction

LVESD, left ventricular end systolic diameter

MCS, mechanical circulatory support

MDMA, 3,4-methylenedioxy-methamphetamine

mmHg, millimeters of mercury

MN, Minnesota

MnSOD, manganese superoxidedimutase

MRA, mineralocorticoid receptor antagonist

MRI, magnetic resonance imaging

MTFCC, MAF/TIGER Feature Class Codes

MI, myocardial infarction

(NAAQS), national ambient air quality standards

NHLBI, National Heart, Lung and Blood Institute

NT-proBNP, N-terminal prohormone of brain natriuretic peptide

NYHA, New York Heart Association

OCD, obsessive compulsive disorder

PGC-1α, proliferator-activated receptor-gammacoactivator-1α

PM, particulate matter

$PM_{2.5}$, particulate matter with diameter less than 2.5 micrometers

PM_{10} particulate matter with diameter between 2.5μm and 10μm

PPCM, peripartum cardiomyopathy

PRL, prolactin

PTSD, post-traumatic stress disorder

REDCap, Research Electronic Data Capture

REP, Rochester Epidemiology Project

ROS, reactive oxygen species

RV, right ventricle / right ventricular

sFlt-1, soluble fms-like tyrosine kinase-1

STAT3, signal transducer and activator of transcription 3

TNFα, tumor necrosis factor alpha

U.S. Environmental Protection Agency (U.S. EPA))

US, United States

VAD, ventricular assist device

VEGF, vascular endothelial growth factor

VEGF-A/B, vascular endothelial growth factors

Wisconsin (WI)

World Health Organization (WHO)

Chapter 1: Introduction

Cardiomyopathies are a group of diseases affecting the heart muscle, or myocardium, characterized by ventricular dysfunction typically due to hypertrophy, inflammation or dilation. This group of diseases contributes significantly to the global burden of cardiovascular disease (CVD). In 2015, approximately 640,000 individuals were diagnosed with cardiomyopathy globally with a reported mortality of more than 350,000 persons.[1] The most common form of cardiomyopathy is dilated cardiomyopathy (DCM), which affects one in 2,500 adults in the United States (US) and presents with the same symptoms as other types of chronic heart failure[2] DCM is the 3rd leading cause of death due to heart failure in the US and the most common cause of heart failure leading to a heart transplant.[3]

One rare and potentially life-threatening type of DCM is peripartum cardiomyopathy (PPCM), which strikes previously healthy women in the last month of pregnancy or up to 5 months after delivery. PPCM is characterized by systolic dysfunction of the left ventricle (LV) leading to dilation and heart failure. PPCM is unique from other cardiomyopathies in that while patients with PPCM have a high morbidity and mortality, these patients can also experience complete recovery of heart function[4,5] with reported recovery rates ranging from 23-90%.[6,7] Early diagnosis and treatment are essential to decrease mortality and increase the potential for full recovery of LV function. However, the symptoms of PPCM (orthopnea, dyspnea, on are very similar to the cardiophysiological changes that occur in a normal pregnancy, making timely diagnosis challenging.[8,9]

Many hypotheses have been suggested regarding the etiology and pathophysiology of PPCM including viral myocarditis leading to DCM, autoimmunity, fetal chimerism, genetics, hemodynamic stresses of pregnancy, nutritional deficiencies and angiogenic imbalance, but the exact causes remain unknown.[10-12] Current research suggests that PPCM may be triggered by hormones secreted by the placenta and pituitary during late gestation that cause a vasculotoxic environment that leads to cardiac dilation and heart failure in susceptible women.[10,13-16] However, why only a small number of women develop cardiomyopathy/ DCM during pregnancy remains unclear and requires further investigation. Other factors that may increase susceptibility to PPCM include oxidative stress, inflammation, viral infection, and antiangiogenic molecules.[17]

There is a well-established relationship between ambient air pollution exposure and the development of CVD.[18-23] Numerous studies have found relationships between elevated criteria air pollutant levels, including particulate matter, ozone, nitrogen dioxide, carbon monoxide, and/or sulfur dioxide, and the development of CVDs including heart failure, stroke, myocardial infarction (MI), coronary artery disease (CAD), hypertension (HT), and cardiac arrhythmias.[19-21,23,24] However, the evidence is strongest for particulate matter sized 2.5 micrometers and smaller ($PM_{2.5}$), which is now recognized as a risk factor for cardiovascular morbidity and mortality.[18,21,22,24,25] Both short- and long-term exposure to $PM_{2.5}$ have been associated with an increased risk of ischemic heart disease, MI, stroke, arrhythmia, and heart failure as well as increased cardiovascular hospitalizations and mortality.[18,22]

One of the main proposed pathways of how exposure to $PM_{2.5}$ leads to heart failure and mortality begins with inflammation and oxidative stress leading to impaired vascular

function, similar to the proposed pathways for the development of PPCM.[22] However, while there is a large amount of evidence that $PM_{2.5}$ exposure contributes to the development and worsening of heart failure there are no studies specifically examining $PM_{2.5}$ exposure and the development of cardiomyopathy or PPCM. In addition to the biological plausibility due to overlapping proposed pathways, multiple systematic reviews and meta-analysis provide epidemiological evidence of a relationship between the two by demonstrating strong positive relationships between exposure to $PM_{2.5}$ and hypertensive disorders of pregnancy, one of the strongest known risk factors for PPCM.[26-28] Based on the known relationship between exposure to $PM_{2.5}$ and CVDs, overlapping potential biological mechanisms, and recent evidence for a relationship between $PM_{2.5}$ exposure and hypertension during pregnancy, we hypothesize that it is possible that $PM_{2.5}$ exposure could be a risk factor for PPCM. If PM exposure is found to be associated with PPCM, this may help us understand why some women are more susceptible to PPCM and why the highest incidence of PPCM occurs in less developed regions of the world like Nigeria, Togo, Haiti, and Pakistan,[6] where indoor cooking and heating involve burning of organic material that releases large amounts of PM. The following aims were developed to test the hypothesis that exposure to elevated levels of air pollution/ $PM_{2.5}$ during and post pregnancy increases the risk of developing PPCM:

Aim 1: Use data from the Rochester Epidemiological Project (REP) to conduct a population-level epidemiological study to determine the incidence and risk factors for PPCM using a well-characterized population in order to estimate the incidence of PPCM among residents of **a)** Olmsted County, Minnesota from 1970 to 2014 (we refer to this part of the study as *REP*) and **b)** the 27 county area including and surrounding Olmstead County

from 1976 to 2014 (we refer to this part of the study as *REP Expanded Region*) in order to determine potential risk factors for PPCM and to determine short- and long-term survival among PPCM patients.

Aim 2: Examine whether an association exists between exposure to air pollution and the incidence of PPCM using either **a)** U.S. Environmental Protection Agency (U.S. EPA) monitored levels of $PM_{2.5}$ or **b)** proxies for air pollution such as traffic density and/or distance from major roadways.

Aim 3: Discuss the **a)** public health implications and **b)** potential policy opportunities that arise from the research results found in Aim 1 and 2.

The rest of this dissertation is laid out as follows: Chapter Two presents a recently published literature review of PPCM by Douglass and Blauwet,[6] a that describes the case definition, epidemiology, pathophysiology, genetics and risk factors, diagnosis, biomarkers, treatment, outcomes, subsequent pregnancy, additional clinical concerns, knowledge gaps, and clinical care points. The reasons for developing a new cohort, of PPCM patients and controls, to test the hypothesis of this dissertation and for using the Rochester Epidemiology Project as the source of this cohort are described in Chapter Three. Chapter Four presents the results of Aim 1a, which are found within a published manuscript but are described in this chapter in more detail.[7] The results from Aim 1b are presented in Chapter Five as a third manuscript which has been published in the *Journal of Cardiac Failure*.[7] Chapter Six examines the relationship of $PM_{2.5}$ exposure and the development of CVD and presents the literature foundation and a proposed mechanism for a relationship between $PM_{2.5}$ exposure and the development of PPCM as well as how Aim 2 had to be reframed due to limitations of available data. And finally, Chapter Seven

presents a case study titled “Clean Air Act: Peripartum Cardiomyopathy and the Rochester Epidemiology Project” which provides results from the modified Aim2 as well as discussion points from Aim 3. This chapter examines the ability of three commonly available methodologies (air monitoring, traffic density, and distance to major roadways) to ascertain the role of PM2.5 exposure on our study cohort, highlights the issues preventing each method from being fully applied, presents policy-based recommendations that would allow studies to successfully determine whether PM2.5 exposure leads to increased susceptibility to developing PPCM, and makes policy recommendation that could strengthen the human health protection required by the Clean Air Act. The final chapter of this dissertation, Chapter Eight, makes overall conclusions about the research project, identifies knowledge and research gaps, and discusses the environmental health implications of the research project presented in this dissertation.

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Chapter 2: Review of the Literature: Peripartum Cardiomyopathy*

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Synopsis:

Peripartum cardiomyopathy (PPCM) is a form of heart failure with no known other cause that occurs towards the end of pregnancy or in the months following pregnancy and is marked by left ventricular systolic dysfunction. The cause of PPCM remains unknown and there is no diagnostic test specific to PPCM. Outcomes vary and include complete left ventricular recovery, persistent cardiac dysfunction, transplant, and death. Numerous advances have been made in understanding the etiology, pathophysiology and natural history of this disease, but many knowledge gaps remain. This article reviews the most recent data and recommendations for clinical practice in addition to highlighting the multiple knowledge gaps related to PPCM that warrant further investigation.

Key Points:

- Diagnosing peripartum cardiomyopathy (PPCM) requires a high degree of suspicion, because presenting signs and symptoms tend to mimic those of normal pregnancy and the early postpartum period.
- Guideline-directed medical therapy for heart failure, with special considerations for use during pregnancy and lactation, is recommended, although efficacy and optimal duration of therapy have not been established.
- Outcomes of both mother and child are generally good, although a subset of women experience chronic heart failure, transplant and/or cardiac death.
- Subsequent pregnancy is not contraindicated in all women with history of PPCM, because risk of cardiac complications associated with future pregnancy varies according to degree of left ventricular recovery.

Abbreviations:

ACE-I, angiotensin-converting enzyme-inhibitor

AHA, American Heart Association

ARB, angiotensin receptor blockers

ARNI, angiotensin receptor neprilysin inhibitor

BMI, body mass index

BNP, brain natriuretic peptide

CCS, Canadian Cardiovascular Society

CRP, C-reactive protein

DCM, dilated cardiomyopathy

ECG, electrocardiogram

Fas/Apo1, Fas/apoptosis antigen 1

GDMT, guideline directed medical therapy

HDP, hypertensive diseases of pregnancy

HFA ESC WG PPCM, Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy

HFrEF, heart failure with reduced ejection fraction

IL-1β, interleukin 1 beta

IL-6, interleukin 6

INF-γ, interferon gamma

IPAC, Investigations of Pregnancy Associated Cardiomyopathy

kDa, kilodalton

LDL, low-density lipoprotein

LV, left ventricular

LVAD, left ventricular assist device

LVEDD, left ventricular end diastolic diameter

LVEF, left ventricular ejection fraction

MCS, mechanical circulatory support

MRA, mineralocorticoid receptor antagonist

MRI, magnetic resonance imaging

NHLBI, National Heart, Lung and Blood Institute

NT-proBNP, N-terminal prohormone of brain natriuretic peptide

NYHA, New York Heart Association

PPCM, peripartum cardiomyopathy

RV, right ventricular

sFlt-1, soluble fms-like tyrosine kinase-1

TNFα, tumor necrosis factor alpha

US, United States

VEGF, vascular endothelial growth factor

Introduction

Peripartum cardiomyopathy (PPCM) is a form of heart failure with no known cause that occurs toward the end of pregnancy or in the months following pregnancy and is marked by left ventricular (LV) systolic dysfunction. Outcomes vary, because most women experience complete LV recovery, but a significant minority experience persistent cardiac dysfunction, transplant, or death.

Case Definition

The National Heart, Lung, and Blood Institute (NHLBI) and the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) Working Group (WG) on PPCM have both published definitions for PPCM.[1,2] (Box 2.1) These two definitions differ in terms of timing of diagnosis and the cutoff for LV ejection fraction (LVEF). Further investigation is needed to determine potential differences between women diagnosed with PPCM using the NHLBI criteria and (1) women who present with previously undiagnosed cardiomyopathy before 1 month before delivery or greater than 5 months postdelivery, and (2) women who present with an initial LVEF greater than 45%, to determine whether or not pathophysiology and outcomes are similar. Having a clear and accurate definition of PPCM is crucial for determining optimal management strategies and prognosis and facilitating collaborative research.

Epidemiology

Estimates of PPCM incidence vary widely around the world, with many of the estimates coming from retrospective single-center cohort studies. Fig. 2.1 presents selected incidence estimates from several countries. The highest reported rates occur in Nigeria,

with 995 cases per 100,000 deliveries, and Togo, with 781 cases per 100,000 deliveries.[3,4] In the United States, nationwide estimates vary from 18 to 103 per 100,000 live births or deliveries.[5-9] Risk factors associated with increased risk of developing PPCM include black African descent, hypertensive diseases of pregnancy (HDPs), multifetal pregnancies, and advanced maternal age.[6,7,10-13]

Pathophysiology, Genetics, and Risk Factors

The cause of PPCM is not fully understood but is most likely multifactorial. Current research suggests that hormones of late pregnancy cause a vasculotoxic environment that, in susceptible women, leads to the development of PPCM.[14,15] High levels of prolactin are secreted from the pituitary gland and can be cleaved into the vasculotoxic, proinflammatory, and proapoptotic 16-kDa form.[16] At the same time, antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) is secreted from the placenta, inhibiting vascular endothelial growth factor and placental growth factor. Both the 16-kDa form of prolactin and sFlt-1 have been shown to cause PPCM in mouse models.[17,18] sFlt-1 levels are significantly increased in women with PPCM, and higher levels at diagnosis are associated with worse out- comes.[19] Women with preeclampsia also have significantly increased sFlt-1 levels, which may at least partially explain why HDP increases risk for PPCM.[20]

A small percentage of women with PPCM have a family history of dilated cardiomyopathy (DCM). Family clustering has also been observed.[21-26] Studies have also shown that a subset of women with PPCM have genetic mutations linked to DCM, predominantly in the *TTN* gene, which encodes the titin protein, which is critical to cardiac muscle structure.[27-29] The Investigations of Pregnancy Associated Cardiomyopathy (IPAC)

study found that 1 *TTN* mutation genotype was associated with lower LVEF at 6 and 12 months, especially in black women, which may help explain why black women have worse outcomes compared with white women.[30] High frequencies of mutations in the *TTN* gene have also been found in women with preeclampsia, which may help to explain the increased risk of PPCM in women diagnosed with HDP.[31] However, only 15% to 20% of women with PPCM have TTN mutations, and greater than 90% of individuals in the general population that have TTN mutations never develop any form of cardiomyopathy,[27-29,32] so the significance of TTN mutations in women with PPCM remains unclear. Other factors that may increase susceptibility for PPCM include oxidative stress, inflammation, viral infection, and antiangiogenic molecules.[33]

Diagnosis

Because the exact cause remains unknown and no single test currently exists to confirm the diagnosis, PPCM remains a diagnosis of exclusion. Women generally present with symptoms that are common to pregnancy (orthopnea, dyspnea on exertion, fatigue, edema, paroxysmal nocturnal exertion, and chest tightness), so the diagnosis of PPCM may be delayed or missed altogether. Late diagnosis has been linked to worse outcomes, including persistent cardiac dysfunction and increased mortality.[13,34-40]

Diagnostic Tests

Echocardiogram, electrocardiogram (ECG), chest radiograph, cardiac MRI, and laboratory testing may all be useful in the diagnosis of PPCM. Echocardiography is the most important imaging modality, because it is readily available in many health care centers and can easily and comprehensively assess cardiac structure and function. By the

NHLBI definition, LVEF must be less than 45%.[1] The left ventricle is usually, but not always, dilated.[33-35,41] Assessment of right ventricular (RV) function is essential, because 3 recent articles have reported that many women with PPCM also have RV dysfunction and that these women are at higher risk for adverse outcomes.[42-44] Additional echocardiographic findings may include RV dilatation, mitral and/or tricuspid valve regurgitation, atrial enlargement, increased pulmonary pressures, and intracardiac thrombus.[33-35,41] Cardiac MRI may be useful for the evaluation of biventricular structure and function or when echocardiography is nondiagnostic, but gadolinium is not recommended for use during pregnancy.[43,45,46] Suggested diagnostic testing is outlined in Table 2.1.

Biomarkers

Many biomarker levels have been shown to be abnormal in women with PPCM and may thus be useful in diagnosing PPCM (Table 2.2). Markers of cardiac function such as N-terminal prohormone of brain natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), and cardiac troponin are likely the most clinically useful. No biomarkers can be used in isolation to confirm PPCM, because none are specific to this disease.

Treatment

Initial Management

Initial management strategies vary depending on pregnancy status (Table 2.3). A multidisciplinary team approach to management is recommended, particularly if the woman is pregnant or in the early postpartum period.

Medical Therapy

Women diagnosed with PPCM should be treated with guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF), bearing in mind the safety of specific medications during pregnancy and breastfeeding. Recommended medications may include b- blockers, angiotensin-converting enzyme inhibitors (ACE-Is)/angiotensin receptor II blocker (ARBs), angiotensin receptor neprilysin inhibitor (ARNIs), hydralazine/nitrates, mineralocorticoid receptor antagonists (MRAs), and diuretics. Anticoagulation should be initiated if LV thrombus is present and may be considered in women with LVEF less than 35%.

Whether or not initiating GDMT for HFrEF is necessary in all women with PPCM remains unclear, because some women recover LV function quickly and completely while taking only minimal to low doses of heart failure medications. Note that there has never been a randomized clinical trial testing the efficacy and safety of any heart failure medications in women with PPCM. Information regarding specific medications and their compatibility with pregnancy and breast feeding is reviewed Karen L. Florio and colleagues' article, "Cardiovascular Medications in Pregnancy: A Primer."[47]

Bromocriptine

Bromocriptine, which inhibits the nursing hormone prolactin, has been proposed as a novel treatment of PPCM in response to the hypothesis that the development of PPCM is driven by the antiangiogenic and proapoptotic 16-kDa cleaved form of prolactin. A small proof-of-concept study with 20 women in South Africa found that the addition of bromocriptine led to greater recovery of LVEF and lower mortality at 6 months.[48] A second

study in Burkina Faso showed that treatment with bromocriptine was associated with increased LVEF at 2 weeks and at 3, 6, and 12 months, as well as decreased mortality.[49] However, both studies had unusually high rates of mortality in the control groups, limiting the ability to generalize the results. A multicenter randomized study with no control group conducted in Germany compared 2 dosing regimens (1 week vs 8 weeks) of bromocriptine in addition to GDMT for heart failure.[50] Both study groups had similar outcomes, with no women undergoing heart transplant and no mortality in either group. The lack of a control group limits the applicability of these results in current clinical practice.

In addition to the lack of rigorous clinical research showing the efficacy of bromocriptine for treatment of acute PPCM, concern regarding potential serious adverse effects has limited routine administration of bromocriptine in clinical practice. Treatment with bromocriptine has been associated with stroke, myocardial infarction, and seizures and, as a result, it is no longer marketed for elective lactation suppression in the United States.[34] If bromocriptine is used, anticoagulation should be administered for the duration of therapy because women are already in a hypercoagulable state during the peripartum period and bromocriptine may further increase hypercoagulability.

Of particular importance, women treated with bromocriptine cannot breastfeed their infants. The World Health Organization recommends exclusive breastfeeding for 6 months and continued breastfeeding for at least 1 to 2 years because of the importance of breastfeeding to the health of both mother and infant. Not breast- feeding is associated with increased risk of diabetes, ovarian and breast cancer, and postpartum depression for mothers, and higher rates of mortality, infections, eczema, asthma, childhood obesity, type 2 diabetes, leukemia, and lower intelligence in children.[51,52] Results of the IPAC study and

two retrospective cohort studies suggest that breastfeeding has no detrimental effect on outcomes for women with PPCM.[53-55]

The most recent statement on PPCM by the HFA ESC WG PPCM lists treatment with bromocriptine as a class IIb recommendation.[41] In contrast, the American Heart Association (AHA) and the Canadian Cardiovascular Society (CCS) both recommend that bromocriptine should not routinely be used in the treatment of PPCM until more rigorous data that support the safety and effectiveness of its use are available.[33,56]

Chronic Management

Most experts agree that GDMT for HFrEF should be continued indefinitely in women with PPCM who have persistent cardiac dysfunction. The optimal duration of treatment of women who recover normal LV function is unknown. A 2016 AHA scientific statement on the diagnosis and treatment of dilated cardiomyopathies recommended indefinite continuation of treatment in women with PPCM, including those with recovered cardiac function, as well as yearly clinical follow-up and assessment of LV function even after recovery.[35] More recent articles suggest that treatment duration should be considered on a case-by-case basis, with changes to or discontinuation of any cardiac medications to be completed slowly using a stepwise approach with frequent clinical and echocardiographic monitoring and follow-up.[34,41] The HFA ESC WG PPCM has published recommendations for women diagnosed with PPCM who have recovered LV function (LVEF>55%) and are New York Heart Association (NYHA) functional class I as follows: continuation of all cardiac drugs for at least 12 to 24 months after full recovery and then discontinue them in a stepwise fashion (first MRA, second ACE-I/ARB/ ARNI, and then β-blocker) with frequent monitoring of symptoms and LV function.[41] Thus, although both

the AHA and HFA ESC WG PPCM guidelines agree that diuretics can be tapered and discontinued if there are no signs of fluid over- load, there is no consensus regarding duration of other cardiac medications in individual women.

Several studies and case reports have shown that some women with PPCM who have recovered LV function can safely be tapered off medical therapy.[36,57-59] In one study, 5 women were tapered off all cardiac medications and none experienced deterioration of LV function over an average follow-up duration of 29 months (range, 5– 63 months).[59] Another report found that 2 women who had fully recovered LV function had deterioration of LVEF after discontinuation of all cardiac medications, with deterioration occurring at 24 and 34 months after diagnosis.[58] Two more recent studies found that women with LV recovery may have high rates of LV diastolic dysfunction and reduced exercise capacity[60] as well as ongoing angiogenic imbalance and residual myocardial injury,[61] suggesting that women who recover may benefit from long-term GDMT for HFrEF.

Long-term cardiology follow-up of women with history of PPCM who have recovered LV function is recommended regardless of whether or not LV recovery occurs and/or cardiac medications are discontinued (see Table 2.1).

Advanced Heart Failure Therapies

Women with PPCM who have severe myocardial disease may benefit from a wearable or implant- able cardiac defibrillator, left ventricular assist de- vice (LVAD), mechanical circulatory support (MCS), and/or transplant. Multiple factors affect the rates of each of these types of advanced heart failure therapy, including time to diagnosis, race, and availability. Rates of use of each of these advanced therapies in women with PPCM are difficult to discern, because studies often do not list these therapies separately and have

combined these outcomes differently for reporting. A nation- wide study conducted in the United States reported that, between 2004 and 2011, 1.5% of patients with PPCM required MCS and 0.5% of patients underwent transplant.[9] Study specific rates in the United States vary between 0% and 7.8% for defibrillator implantation, 0% to 17.2% for MCS (intra-aortic balloon pump, LVAD, and extracorporeal membrane oxygenation), and 0% to 8.8% for transplant.[11,36,40,62-64] Rates in other countries vary widely, often depending on the availability of these advanced treatment options.[39,57,64-72]

Outcomes

Mortality

Women with PPCM tend to have lower mortalities than women with other forms of DCM.[73,74] Re- ported mortalities related to PPCM vary widely both within and between countries and within similar follow-up durations (Table 2.4). A recent systematic review and meta-analysis by Kerpen and colleagues[75] found the overall PPCM mortality to be 9%, with higher rates in developing countries (14%) compared with more advanced countries (4%). Fig. 2.2, which includes 9 countries in addition to the 13 included in the meta-analysis by Kerpen and colleagues,[75] shows a similar trend of higher mortalities in developing countries. The higher PPCM mortalities in developing countries are most likely related to the impact of social determinants of health, including reduced access to care in general and access to advanced heart failure therapies in particular.

Mortalities in Taiwan and the United States seem to be exceptions among advanced countries, whereas rates in The Philippines, China, and Singapore do not follow the trend among developing countries. Small sample sizes[76-78] and differences in methodologies and

populations, particularly among the US reports,[7-9,11-13,36,38,40,43,59,62,63,73,74,79-88]may account for these variations.

Left Ventricular Recovery

Similar to mortality, women with PPCM tend to have higher rates of LV recovery than women with other forms of DCM.[73,74] Recovery rates differ between countries, from 28% in Haiti[89] to 43% in Israel,[72] 48% in Turkey,[90] 47% in Germany,[29] 55% in South Africa,[91] 63% in Japan,[68] and 67% in Denmark.[65] There is a wide variation in recovery rates within the United States as well, with reported rates ranging between 23% and 72%.[38,40,59,62,79,85,87,92,93] Lack of consensus in the definition of LV recovery (LVEF>45% vs 50%, vs 55%, or any recovery vs a specific percentage increase in LVEF) and follow-up time (6 months vs 12 months vs longer) contributes to the large range in reported LV recovery rates among studies across the globe.

Timing of LV recovery varies, with some women recovering in days to weeks, whereas other women require months to years. An article from Israel reported that 22% of women with PPCM achieved full recovery (LVEF ≥50%) within 2 weeks, a further 30.1% recovered by 1 year, and an additional 13.8% recovered between 1 and 10 years.[72] The mean time to recovery in a study of 44 women in the United States was 54 months.[87] In Haiti, reported recovery time ranged from 3 to 38 months and in Turkey from 3 to 42 months (mean, 19.3 months).[70,94] One study completed in the United States found that 83% of women who recovered did so after more than 6 months of follow-up, whereas another study re- ported that 25% of women who recovered did so between 2 and 8 years after

diagnosis.[85,95] The wide range of time to LV recovery underlines the importance of long-term cardiac follow-up of women with PPCM.

Predictors of Outcome

Many factors have been evaluated for their potential to predict outcomes in PPCM, particularly the risks for persistent myocardial dysfunction and death. The most reliable predictor has been found to be LVEF at diagnosis, with studies consistently reporting that women with lower LVEF (particularly <30%) at diagnosis are less likely to recover and more likely to experience adverse outcomes, including death.[29,36,38,40,58,59,62,79,81,84,87,92,93,96,97] Studies have also reported that the degree of LV dilatation may be a useful predictor, with larger LV end- diastolic diameter (LVEDD) being associated with lack of LV recovery and death.[29,40,58,59,79,93,97,98] LV dilatation and LVEF were combined as predictors in the IPAC study, which found that 91% of women with LVEF greater than or equal to 30% and LVEDD less than 60 mm recovered.[40] The IPAC study also reported that LV global longitudinal strain at presentation was associated with clinical outcomes and may be useful for risk stratification in addition to LVEF.[99] RV fractional area change at diagnosis was shown to be a strong predictor of outcomes in the IPAC study,[44] whereas another study in the United States found that moderate to severe RV dysfunction was associated with more severe disease and higher risk of adverse outcomes.[43] T-wave abnormalities on ECG have been suggested as a useful tool for predicting adverse outcome in PPCM, which could be advantageous in resource-poor settings in which echocardiographic evaluation may not be readily available.[91,100]

Other factors that also seem to affect outcomes include race, HDP, and body mass index (BMI). Studies in the United States show that, compared with nonblack women, black women have worse outcomes, including slower and less complete recovery of LV function and higher rates of defibrillator use, transplant, and mortality.[36,40,62,92,101-104] A recent meta-analysis found that studies with higher rates of African women tend to have higher mortalities.[75] History of HDP during index pregnancy may also be important, with multiple studies finding an association between HDP and improved rates of recovery and reduced mortality.[29,40,53,65,68,95,98,105] The IPAC study found that higher BMI is associated with less cardiac recovery at 6 and 12 months,[106] whereas a study including predominantly black African women in South Africa found that lower BMI was associated with a worse combined end point of death, LVEF less than 35%, or remaining in NYHA functional class III/IV at 6 months.[107] Women with multiple predictors of poor outcome may be at increased risk of persistent cardiac dysfunction and death, but this re- mains speculative because of limited data. Multiple biomarkers have been investigated for their potential usefulness in predicting which women are more likely to experience adverse out- comes, but none have been validated for clinical use (see Table 2.2).

Subsequent Pregnancy

Many women with history of PPCM desire to become pregnant again. One recent study found that 74% of women diagnosed with PPCM desire to have more children and 1 in 4 women with PPCM who are sexually active were not using birth control.[108] All women with PPCM are at risk of declining LV function during subsequent pregnancy, but the risk is not necessarily prohibitive. Although some women experience worsening LV function or even death with subsequent pregnancy, others are able to complete a subsequent

pregnancy without cardiac complications. Having 1 subsequent pregnancy without heart failure relapse does not ensure that a woman will not experience worsening heart function during a future subsequent pregnancy and vice versa.[84,109-111] At present, there is no clear method to identify with certainty which women will experience adverse cardiac events with subsequent pregnancies. The risk of heart failure relapse is highest in women who have persistent LV dysfunction at the onset of a subsequent pregnancy, with up to 50% having further decline in LV function during subsequent pregnancies.[112-115] Women with recovered LV function have an approximately 20% chance of heart failure relapse as defined in various studies by either experiencing heart failure symptoms and/or decrease in LVEF.[109,112-115]

The AHA, the CCS, and the HFA ESC WG PPCM stratify recommendations regarding sub- sequent pregnancy based on LV function, recommending that women with partial or fully recovered LV function be advised that they may consider subsequent pregnancy, whereas women with lack of LV recovery should be advised against subsequent pregnancy.[35,56,114] Despite these recommendations, studies show that only 59% to 75% of women diagnosed with PPCM report receiving counseling on the risk of subsequent pregnancy.[108,116] Importantly, qualitative studies have shown that women report feeling that the counseling provided tends to be limited, with women simply being told that they should not get pregnant again rather than engaging in an informed discussion with a health care provider.[117,118] These findings indicate that discussions regarding contraception and potential risks of subsequent pregnancy should occur with informed health care providers who can provide accurate information and are willing to participate in a shared decision-making process.

All women considering or undergoing subsequent pregnancy, regardless of cardiac function before conception, should be closely monitored by a multidisciplinary team from before conception through to several months postpartum in order to identify potential cardiac compromise as early as possible so as to optimize management and improve outcomes.[35,112,114] Recommended cardiac monitoring includes clinical evaluation, BNP or NT-proBNP, and echocardiogram either just before conception or within the first trimester, at 6 months' gestation, 9 months' gestation, before hospital discharge after delivery, and 1 month after delivery, with the timeline and type of follow-up adjusted according to the patient's clinical status.

Additional Clinical Concerns

Infant Outcomes

The few studies of PPCM that include infant outcomes suggest that PPCM diagnosis in mothers is related to increased adverse outcomes in the infants, including higher rates of preterm and premature birth,[13,88,119,120] increased risk of being born small for gestational age,[13,119] increased rates of low birth weight,[13,88,119,120] and lower Apgar scores at both 1 and 5 minutes.[13,88,119] In women with PPCM, rates of premature birth (<37 weeks' gestation) vary between 25% and 60%[13,38,88,105,120] and are significantly increased compared with controls (25.4% vs 8.6% P<.01119 and 27.9% vs 7.3%; P<.00113). Mean birthweight for infants born to mothers with PPCM ranged between 2378 and 3178 g,[13,38,57,65,72,77,79,85,88,119,120] and two studies with controls found that birth weights were significantly lower in infants born to mothers with PPCM (2697 vs 3165 g, P<.002[119]; and 3188 vs 3331 g, P<.01[120]). Two studies that examined Apgar scores at 1 and 5 minutes

found both to be significantly lower in infants born to mothers with PPCM compared with those born to mothers without PPCM.[13,119]

Premature birth, low birth weight, and lower Apgar scores are all known to be associated with greater risk of infant mortality and a variety of early and late developmental and other medical issues.[121] However, information regarding these outcomes in children of women with PPCM remains limited because infant outcomes in PPCM have only rarely been assessed in research studies.

Mental Health

Depression is a well-known risk factor for heart disease, and depression and anxiety are linked to worse outcomes in heart failure.[122,123] Women diagnosed with PPCM tend to be young mothers who were previously in the prime of their lives and now must juggle a diagnosis of heart failure while caring for a newborn, a household, and possibly other children. These stresses increase the risk for mood disorders. High levels of generalized anxiety, cardiac anxiety, and quality-of-life concerns are present in more than 50% of women with PPCM, and 56% of women with PPCM never return to their baseline emotional states after PPCM diagnosis.[116] Although only 3% to 7% of women with PPCM have a history of depression before PPCM diagnosis,[9,65,81] the rate of depression in women after diagnosis with PPCM has been reported to be 32.3%,[124] which is higher than the reported rate of 11.5% among postpartum women in the United States.[125] Notably, there has been an association reported between depression and lower adherence to appointments for PPCM.[124] Qualitative studies suggest that an underlying issue for ongoing emotional and mental distress is lack of inclusion of the women and their partners in discussions and

decisions related to the women's care and prognosis, with 35% of women in one study thinking that they had not been adequately counseled and another 33% thinking they were left with unaddressed questions.[116-118,124,126,127]

The HFA ESC WG PPCM and AHA both advise that each woman with PPCM be assessed and followed during subsequent pregnancy by a multidisciplinary team including cardiology, obstetrics, maternal-fetal medicine, neonatology, anesthesiology, and possibly other specialties.[35,114] Given the high incidence of mood disorders in women with history of PPCM, including mental health specialists or social workers on the multidisciplinary team to help address the long lasting emotional and psychological impact of PPCM would be beneficial, not only during subsequent pregnancy but after initial diagnosis as well.

Summary

Although rare, PPCM can have a profound effect on previously healthy young women. Numerous advances have been made in understanding the cause, pathophysiology, and natural history of this disease, but many knowledge gaps remain (Box 2.2). Large prospective studies and randomized clinical trials are needed to address these knowledge gaps and to facilitate development of evidence-based guidelines regarding the diagnosis and management of PPCM. In addition, it is of utmost importance that management decisions regarding women with PPCM be formulated among a multidisciplinary team using a shared decision-making approach with the patients and their families in order to optimize diagnosis, treatment, and outcomes for all concerned.

Clinical Care Points

- Women diagnosed with PPCM benefit from evaluation and treatment by a multidisciplinary team including members from cardiology, maternal fetal medicine, obstetrics, social work, mental health and other specialties as indicated.
- Obtaining a complete patient and family cardiac history is important in order to establish the diagnosis of PPCM, as PPCM is a diagnosis of exclusion.
- Clinicians should have a low threshold for obtaining cardiac testing, including an ECG, echocardiogram, and B-type natriuretic pep- tide (BNP) or N-terminal proBNP, in pregnant/postpartum women who present with signs/symptoms suggestive of heart failure, even though the signs/symptoms may seem typical for women who are pregnant or postpartum.
- No biomarkers, including troponin T, troponin I, B-type natriuretic peptide (BNP) or N-terminal proBNP, are specific for the diagnosis or PPCM.
- Bromocriptine may be helpful for treatment of acute PPCM, particularly in postpartum women with severely depressed LVEF, but the safety and efficacy of this medication for treatment of PPCM has not yet been established.
- Clinicians must be cognizant of which of the guideline directed mediations for heart failure are safe to use during pregnancy and which are safe to use during lactation.
- Contraceptive counseling during the post- partum period and on a regular basis there-after is imperative in order to prevent unplanned pregnancy.

- Women with history of PPCM should be counseled about the risk of subsequent pregnancy, bearing in mind that women who have recovered normal LV function are generally able to complete a subsequent pregnancy without significant complications.
- Screening women with PPCM for anxiety and depression in both in the acute and chronic care setting is essential for optimizing management of their mental and physical health.

Additional References for figures: [128-164]

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Table 2.1 Suggested evaluation for women with peripartum cardiomyopathy

Time Period[a]	History and Clinical Examination	Laboratory Tests[b]	Urinalysis[c]	Chest x-ray	Chest CTA[d]	ECG	ECHO	Cardiac MRI[e]
Diagnosis	♥♥♥♥	♥♥♥♥	♥♥	♥♥♥♥	♥♥	♥♥♥♥	♥♥♥♥	♥
3 months	♥♥♥♥	♥♥♥♥				♥♥♥♥		
6 months	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
12 months	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
18 months	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
24 months	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
>24months[f]	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	

♥♥♥♥ highly recommended, ♥♥ recommended in certain circumstance, ♥ considered in certain circumstances

Abbreviations: CTA, computed tomography angiography; ECG, electrocardiogram; ECHO, echocardiogram.
[a]Timing of follow-up may vary according to presentation and clinical course.
[b]Suggested laboratory tests include complete blood count, basic metabolic panel, and brain natriuretic peptide (BNP) or N-terminal prohormone of BNP (NT-proBNP) at all times points plus aspartate aminotransferase, alanine aminotransferase, cardiac troponin, and thyroid stimulating hormone at baseline and during follow-up, if indicated.
[c]Urinalysis is especially important for women presenting with increased blood pressure during pregnancy or the first 6 weeks postpartum to assess for preeclampsia.
[d]Consider chest CTA to assess for pulmonary embolism in patients presenting during pregnancy or the first 6 weeks postpartum.
[e]Consider cardiac MRI if patient presents during the postpartum period and echocardiography results are inconclusive.
[f]Annual follow-up should occur indefinitely

Table 2.2 Biomarkers in peripartum cardiomyopathy

Biomarkers of Cardiac Function		
NT-ProBNP	May be increased[29,138,154]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
BNP	May be increased[104]	Higher levels at diagnosis are associated with persistent LV dysfunction[104,138] Higher levels at 6 mo are associated with persistent LV dysfunction[104] Higher levels at 6 mo may predict mortality[89,138] Increased levels at 3 and 6 mo may predict persistent dysfunction[69] Lower levels at 3 and 6 mo are associated with faster recovery[69]
Cardiac troponin	May be increased[154]	Higher levels at diagnosis are associated with persistent LV dysfunction[156]
Biomarkers of Inflammation		
C-reactive protein	May be increased[95,138,154,157]	Higher levels at baseline may predict mortality[157] Higher levels at baseline are correlated with worse disease[95] Increased levels at 3 and 6 mo may predict persistent dysfunction[69]
IL-6	May be increased[138,157]	Higher levels at baseline may predict mortality[157]
Tumor necrosis factor alpha	May be increased[95,138,157]	Higher levels at baseline may predict mortality[157]

IL-1b	May be increased[138]	—
Interferon gamma	May be increased[138]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
Pregnancy and Nursing Hormones		
Relaxin-2	May be decreased[158,159]	Higher levels at diagnosis are associated with recovery at 2 mo[19]
Prolactin	May be increased[138]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
Vasculotoxic Cause–related Biomarkers		
Oxidized low-density lipoprotein	May be increased[16,138]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
Fas/apoptosis antigen 1	May be increased[95,138]	Higher levels at baseline may predict mortality[95]
sFlt-1	May be increased[18]	Higher levels at diagnosis are associated with more severe disease and major adverse events[19,60]
Asymmetric dimethyl arginine	May be increased[29]	—
PlGF	May be increased[159]	—
sFlt1/PlGF ratio	May be low[159]	—
Plasminogen activator inhibitor-1	May be increased[160]	—
MicroRNAs		
miR-146a	May be increased[29,161]	—
miR-1991	May be increased[162]	—
Biomarkers of Fibrosis and Remodeling		

Galectin-3	May be increased[102]	High baseline levels are associated with poor outcomes[102]
Soluble ST2	May be increased[102]	High baseline levels are associated with poor outcomes[102]
Cleaved osteopontin	May be increased[102]	High baseline levels are associated with poor outcomes[102]
Matrix-metallo-proteinase-2	May be increased[138]	—

Abbreviations: IL, interleukin; PIGF, placental growth factor.

Data from references: [16,18,18,29,60,89,95,96,102,104,138,154,156-160,162]

Table 2.3 Initial management of peripartum cardiomyopathy

	 **Hemodynamically stable**	 **Hemodynamically unstable**	 **Hemodynamically stable**	 **Hemodynamically unstable**
Consult Cardio-Obstetrics specialist				
Consult High-Risk Obstetrics (Maternal Fetal Medicine) specialist			–	–
Form multidisciplinary team to prepare delivery plan			–	–
Consider early delivery	–		–	–
Arrange for fetal monitoring during labor and delivery			–	–
Initiate selected oral heart failure medications (e.g., diuretics, nitrates, hydralazine, digoxin)			–	–
Initiate oral GDMT for HFrEF [e.g., beta blocker, ACE-I, ARB, ARNI, MRA, diuretics (modify if lactating)]	–	–		 (after stabilized)
Consider using inotropes	–		–	
Initiate anticoagulation if LV thrombus				
Consider anticoagulation if LVEF <35%	–	–		
Plan for vaginal delivery		–	–	–

Plan for probable Cesarean delivery	–		–	–
Provide supplemental oxygen and/or noninvasive ventilation, if hypoxic		–		–
Intubate and ventilate if hypoxic despite noninvasive ventilation	–		–	
Consider advanced heart failure therapies[a] if failure to respond to medical therapy (and delivery)	–		–	
Discuss lactation preferences	–	–		–
Discuss contraception	–	–		

[a]Mechanical circulatory support/ventricular assist device/cardiac transplant

Abbreviations: ACE-I, ACE inhibitor; ARB, angiotension receptor blocker; ARNI, angiotension receptor neprolysin inhibor; GDMT, guideline directed medical therapy; HFrEF, heart failure with reduced ejeciton fraciton; LV, left ventricular; LVEF, left ventricular ejeciton fraction

Table 2.4 Studies with ≥50 subjects reporting mortality among women with PPCM

First Author	Follow-up duration	Actual, mean, median	Country	Data Source	Study Years	Sample (n)	Mortality (%)
In Hospital							
Kolte et al,[9] 2014	NA	NA	United States	Nationwide Inpatient Sample database	2004-2011	34,219	0.0%
Krisnamoorthyet al,[80] 2016	NA	NA	United States	Nationwide Inpatient Sample database	2009-2010	4871	0.0%
Lee et al,[136]2018	NA	NA	South Korea	Korean National Health Insurance Database	2010-2012	795	1.0%
Masoomi et al,[8]2018	NA	NA	United States	Nationwide Readmission database	2013	568	1.2%
Kao et al,[11] 2013	NA	NA	United States	Inpatient administrative databases for 6 states	2003-2007	535	1.3%
Mielniczuk et al,[7] 2006	NA	NA	United States	National Hospital Discharge Survey	1990-2002	16,269	1.9%
1-6 Months							
Azibani et al,[102]2020	6 months	actual	Germany	1 hospital	Missing	73	0.0%
Dhesi et al,[119]2017	6 months	actual	Canada	Multiple databases linked together covering all of Alberta	2005-2014	194	1.5%
Huang et al,[154]2012	21.6 days	mean	China	1 hospital	2007-2009	52	1.9%
Tibazarwa et al,[90] 2012	6 months	actual	South Africa	1 hospital	2003-2008	78	3.8%
Libhaber et al,[97] 2015	6 months	actual	South Africa	2 hospitals	Missing	206	12.6%
Blauwet et al,[106] 2013	6 months	actual	South Africa	1 hospital	Missing	162	13.0%
Azibani et al,[102] 2020	6 months	actual	South Africa	1 hospital	Missing	56	14.3%
Sliwa et al,[95] 2006	6 months	actual	South Africa	1 hospital	Missing	100	15.0%

7-12 Months							
Kamiya et al,[67]2011	9.6 months	mean	Japan	Nationwide survey of medical locations	2007-2008	102	3.9%
Isezuo et al,[3]2007	9.7 months	mean	Nigeria	1 hospital	2003-2005	65	12.3%
1-2 Years							
Phan et al,[79]2020	1 year	actual	United States	Southern California Kaiser Healthcare System	2003-2014	333	0.3%
Erbsoll et al,[64]2017	10-14 months	actual	Denmark	Danish National Patient Register, Medical Birth Registrar, Causes of Death Registrar	2005-2014	61	1.6%
McNamara et al,[40] 2015	1 year	actual	United States	IPAC - nationwide cohort of 100 women	2009-2012	100	4.0%
Goland et al,[12] 2013	1.6 years	mean	United States	2 hospitals	1993-2000	156	7.1%
Wu et al,[39] 2017	1 year	actual	Taiwan	National health insurance database	1997-2011	742	7.3%
Elkayam et al,[38] 2015	1.9 years	mean	United States	Survey mailed to doctors nationwide & data from 1 hospital	Missing	100	9.0%
Sliwa et al,[140]2011	2 years	actual	South Africa	1 hospital	Missing	60	36.7%
>2 Years							
Amos et al,[58]2006	3.6 years	mean	United States	1 hospital	1990-2003	55	0.0%
Habli et al,[78]2018	3.4 years	mean	United States	2 hospitals	2000-2006	70	0.0%
Li et al,[104] 2016	3.6 years	mean	China	1 hospital	2004-2011	71	0.0%

Moulig et al,[152] 2019	5 years	actual	Germany	1 hospital	2006-2013	66	1.5%
Gunderson et al,[13] 2011	3 years	actual	United States	Northern California Kaiser Delivery Hospitals	1995-2004	110	1.8%
Peters et al,[43]2018	3.6 years	median	United States	1 hospital	1992-2016	53	1.9%
Brar et al,[81]2007	4.7 years	mean	United States	Southern California Kaiser Healthcare System	1996-2005	60	3.3%
Ekizler et al,[163] 2019	5.6 years	median	Turkey	1 hospital	2009-2017	82	7.3%
Pillarisetti et al,[84] 2014	2.9 years	mean	United States	2 hospitals	1999-2012	100	11.0%
Fett et al,[150]2005	2.2 years	mean	Haiti	1 hospital	2000-2005	98	15.3%
Akil et al,[66]2016	2.7 years	mean	Turkey	3 hospitals	2002-2012	58	15.5%
Harper et al,[62]2012r	7 years	actual	United States	1 hospital	2002-20030	85	16.5%
Biteker et al,[69]2020	3.4 years	mean	Turkey	1 hospital	2005-2016	52	19.2%
Mahowald et al,[61] 2019	6.3 years	mean	United States	1 hospital	2000-2011	59	20.3%
Mishra et al,[145] 2006	6.1 years	mean	India	1 hospital	1995-2005	56	23.2%

Abbreviations: NA, not available

Data from references:[3,7–9,11–13,38-40,43,58,61,62,64,66,69,78,79,81,84,90,95,97,102,104,106,119,136,140,145,150,152,154]

Figure 2.1

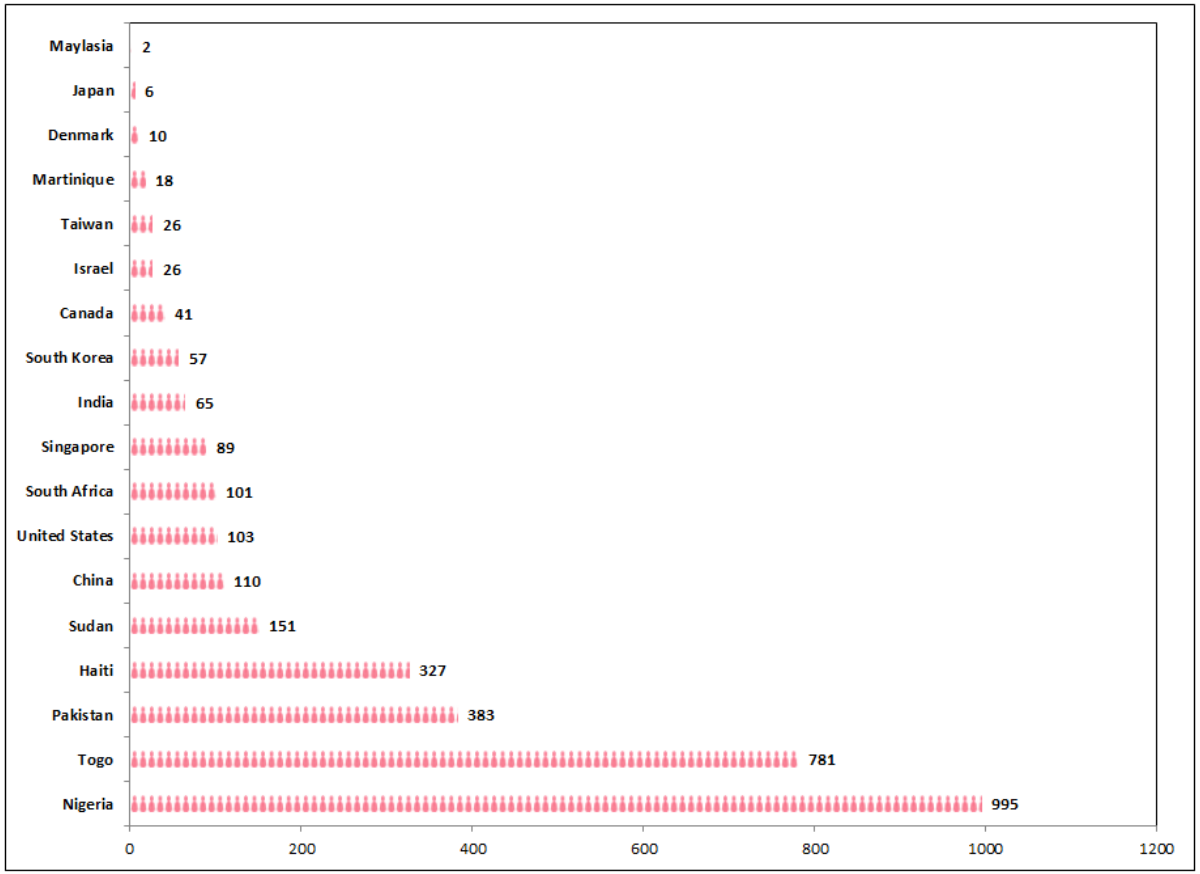

Figure 2.1 Incidence of peripartum cardiomyopathy (per 100,000 live births or deliveries.)
Measurements using live births: Hati[127], USA[9], Singapore[77], India[128], Canada[119], Martinique[129], Japan[130], Malaysia[131]. Measurements using deliveries: Nigeria[3], Togo[4], Pakistan[132], Sudan[133], China[134], South Africa[135], South Korea[136], Israel[118], Taiwan[39], Denmark[64]. Data from references[3,4,9,39,64,77,118,119,127-136].

Figure 2.2

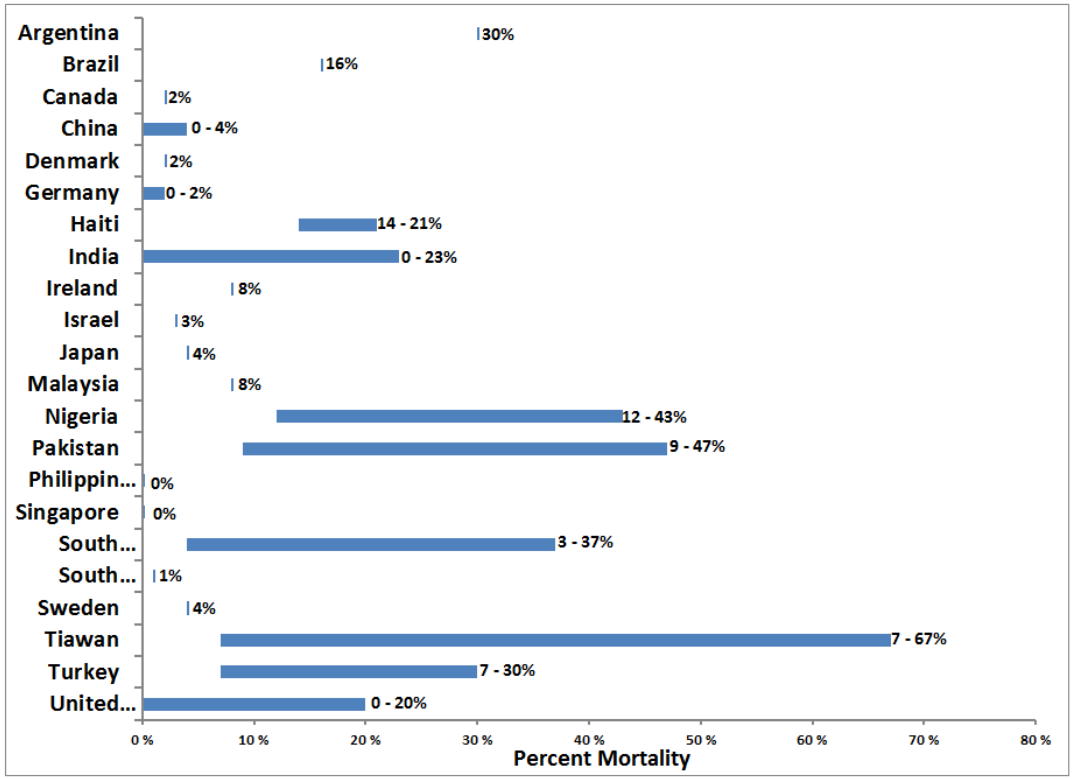

Figure 2.2 Percent mortality estimates for peripartum cardiomyopathy.

Twenty-four countries are represented 12 of which only had one estimate available while each of the other 10 countries had between 2 and 25 estimates available. For countries with only 1 estimate available, that value is indicated. For the countries with multiple estimates available ranges are presented showing the highest and lowest estimate for each country. Data from References:[7–9,11–13,36,38–40,42,43,47,56–58,61,62,64–70,73,75–87,95,97,99,102,106,119,131,136–155b] References: US[7-9,11-13,36,38,40,43,58,61,62,72,73,78-87], Turkey[57,66,69,85,96,99,137], Taiwan[39,75], Sweden[56], South Korea[136], South Africa[47,65,95,97,102,106,138-141], Singapore[77], Philippines[76], Pakistan[142,143], Nigeria[42,144], Malaysia[131], Japan[67], Israe[171], Ireland[68], India[145-148], Haiti[149-151], Germany[102,152], Demark[64], China[153,154], Canada[119], Brazil1[55], Argentina[70].

Box 2.1 Current peripartum cardiomyopathy definitions

National Heart Lung and Blood Institute (NHLBI)1

- Development of cardiac failure in the last month of pregnancy or within 5 months of delivery
- Absence of an identifiable cause for the cardiac failure
- Absence of recognizable heart disease before the last month of pregnancy
- LV systolic dysfunction identified by classic echocardiographic criteria, such as ejection fraction < 45% or fractional shortening < 30%, or both

European Society of Cardiology (ESC)2

- Heart failure secondary to LV systolic dysfunction with an LV ejection fraction < 45%
- Occurrence toward the end of pregnancy or in the months following delivery (mostly in the months following delivery)
- No other identifiable cause of heart failure

Data from Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. Jama. 2000;283(9):1183-1188 and Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a
position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. European journal of heart failure. 2010;12(8):767-778.

Box 2.2 Knowledge gaps in peripartum cardiomyopathy requiring further evidence-based investigation

Research questions

Diagnosis

- How can women who are susceptible to developing PPCM be identified before pregnancy?

Pathophysiology and genetics

- What is the exact pathophysiology/pathophysiologies of PPCM?
- To what extent to do genetic variations contribute to the development of PPCM and influence outcomes?

Diagnosis

- Is there a PPCM-specific biomarker, or set of biomarkers, that can be used to diagnose PPCM with a high degree of certainty?

Treatment

- Which, if any, typical heart failure medications are beneficial for treating all women with PPCM?
- How long should GDMT for HFrEF be continued in women with PPCM who have completely recovered LV function?
- Is bromocriptine safe and effective for treatment of acute PPCM?
- When is the use of wearable defibrillators indicated?
- When should an implantable cardioverter defibrillator be recommended?
- What is the most appropriate type and timing of follow-up in women who have recovered LV function versus those who have not?

Outcomes

- What are the best clinical predictors of outcome for women with PPCM that could be available in various health care resource settings?
- What are the very-long-term (ie, decades after diagnosis) outcomes for women with history of PPCM?

Subsequent pregnancy

- What are the risks of cardiac deterioration and death with subsequent pregnancy with women with history of PPCM and those who have recovered LV function versus those who have not?
- Are there management strategies that are useful to reduce the risk of adverse outcomes in women during a subsequent pregnancy?

Infant outcomes

- What are the short-term and long-term health risks for infants born of mothers with PPCM?
- Are there strategies than can mitigate these risks? Mental and emotional health
- Are there safe and effective strategies that can be used to decrease the burden of mental and emotional health issues affecting women with PPCM and their families?

Issues to be addressed in order for future research to adequately address knowledge gaps

- Global agreement on the definition of PPCM
- Global agreement on the definition of LV recovery
- Global agreement on the definition of relapse during subsequent pregnancy
- Funding for large, multicenter, well-designed, and well-adjudicated prospective registries and clinical trials

Chapter 3: The Rochester Epidemiology Project and the Study Cohort

To further study PPCM and the role possible environmental exposures might play we created a case-control cohort using the Rochester Epidemiology Project (REP).[1] Previously published studies of PPCM in the US included single or multi-institution cohorts and a few population level studies using nationwide databases with limited data sets such as the National Hospital Discharge Survey, The National Inpatient Survey from the Healthcare Cost and Utilization Survey.[2,3]

The population level studies are limited by the use of diagnosis codes for identifying cases, which can lead to misclassification, as well as by what data was available as part of the databases. The institution-based studies were more likely to use medical records review to confirm cases, but were limited to data available through their institution(s). To overcome these limitations for our study we chose to create a new cohort using the REP, which to our knowledge, is the first population level incidence study with complete medical record review to confirm cases and abstract data.

The REP is a unique resource in that it is one of the few places that allows for "population-based" research to be conducted and true population level incidence estimates. The REP, which had been federally funded for over 50 years, is a collaboration between health care providers, medical facilities, and community members that links medical records from almost all health care providers in Olmsted County, including Mayo Clinic and Olmsted Medical Center, and their affiliated hospitals as well as local private providers.[4-6] The healthcare providers who have agreed to participate in the REP share

medical records which are all assembled in a large database. The results is a databased linking medical records form essentially all source of medical care available to, and utilized by, the Olmsted County population as well as a large portion of the care available to, and utilized by, residents of the surrounding counties. These records therefore contain the details of every inpatient hospitalization, every outpatient visit to the offices, clinics or emergency rooms in the county, every physician visit to nursing homes or private homes, as well as every laboratory result, pathology report (including autopsies), imaging report and correspondence pertaining to individual patients. The REP also has electronic indexes that include demographic information, diagnostic and procedure codes, health services use data, outpatient drug prescriptions, laboratory test results, imaging and procedure reports, and information about smoking, height, weight, and body mass index.[5,7] Both paper and electronic medical records are accessible with a system that lists all record available for each resident of the area.[8] This is an incredibly rich data source allowing for high quality medical research at a population level that has been shown to be generalizable to all of the Minnesota/Wisconsin area, as well as a large segment of the US population.[7,9]

The REP covers 27 counties in southern Minnesota (MN) and western Wisconsin (WI) and can be broken into three overlapping, areas with varying levels of coverage of medical records. (Figure 3.1) The first is Olmsted County alone, which has near complete coverage (99.9%) allowing for very accurate population level incidence estimates, where 98% of residents have agreed to participate in the REP and 90-96% off all health care received by county residents is provided by participating providers with data available from January 1, 1970 through December 31, 2020.[7] The second area is a 7-county region which includes Olmsted County and 6 surround counties and has a 93.8% coverage rate (data

available from January 1 1976 through December 31, 2020) and the largest area (all 27 counties including Olmsted County) has a 60.9% coverage rate (data available from January 1, 2010 through December 31, 2020).[7] The lower coverage rates in the 27-country region is predominantly due to not all health care facilities in the region collaboration with the REP.[7]

Using the REP as our data source we were able to create, to our knowledge, the first population level incidence study with complete medical record review to confirm cases and abstract data. Using the REP data we first conducted a study of cases of PPCM in Olmsted County diagnosed between January 1, 1970 and December 31, 2014 and identified 15 unique cases resulting in an incidence of 20.3 cases per 100,000 live births. This result is reported in a published manuscript *Douglass EJ, et al. A Case-Control Study of Peripartum Cardiomyopathy Using the Rochester Epidemiology Project. J Card Fail. 2021 Feb;27(2):132-142.doi: 10.1016/j.cardfail.2020.12.021. Epub 2021 Jan 1. PMID: 33388468.*[10] More information on the collection of the data from this population level cohort is presented in Chapter 4 of this dissertation. We then expanded the study to include the entire 27 county region of the REP in order to increase the number of cases (48 total) and add controls matched 2:1 on age, race, and number of infants delivered during index pregnancy (pregnancy when diagnosed with PPCM or matched pregnancy in controls). The results from the 48 cases and 96 controls are described in Chapter 5 as a manuscript that has been published in the *Journal of Cardiac Failure*: *Douglass EJ, et al. A Case-Control Study of Peripartum Cardiomyopathy Using the Rochester Epidemiology Project. J Card Fail. 2021 Feb;27(2):132-142.doi: 10.1016/j.cardfail.2020.12.021. Epub 2021 Jan 1. PMID: 33388468.*[10]

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Figure 3.1.

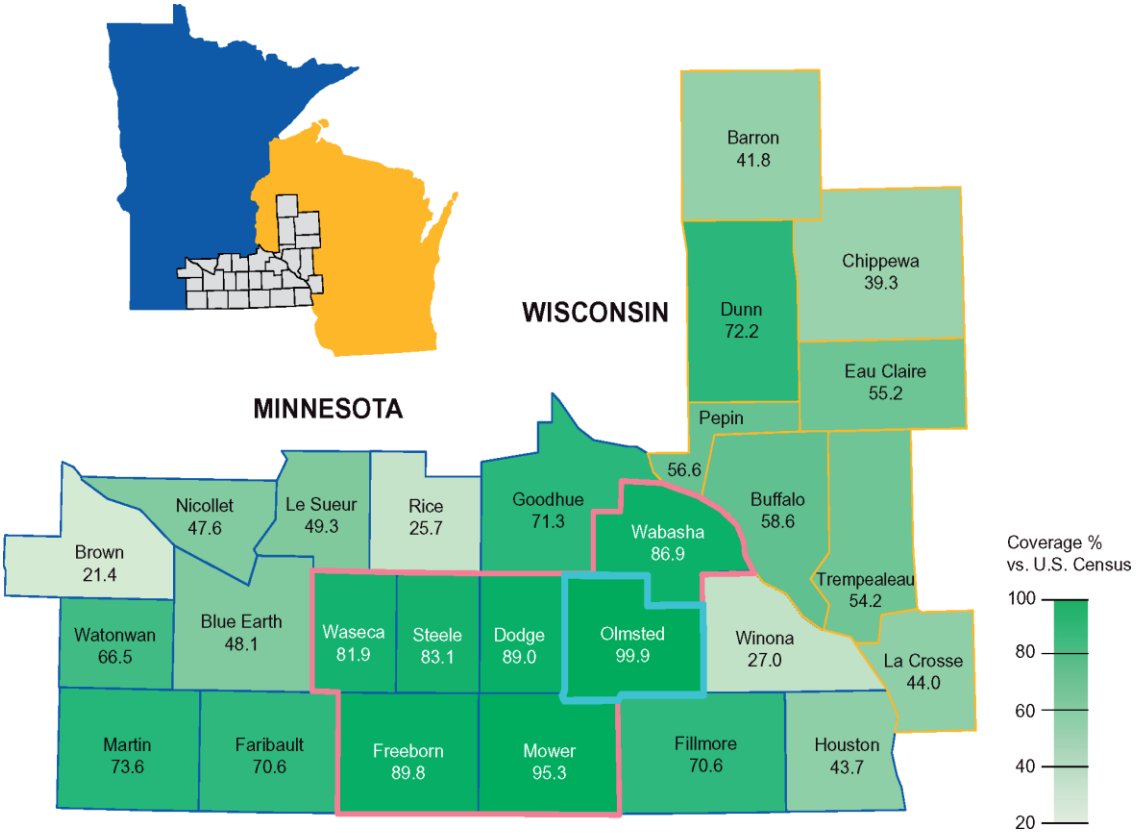

Figure 3.1 Map of the Rochester Epidemiology Project.

Geographical map of the 27-county region showing the geographical location and the percentage capture for each county (black numbers or white numbers). The region can be subdivided into a maximum capture segment, Olmsted County (blue border), a high capture segment, including Olmsted County and six additional contiguous counties (pink border), and the overall 27-county region. The color shading of the counties is proportional to the percentage capture of the E-REP as compared with the US Census estimates

Figure and legend from: Rocca, WA. et al. Data Resource Profile: Expansion of the Rochester Epidemiology Project medical records-linkage system (E-REP). Int J Epidemiol, Volume 47, Issue 2, April 2018, Pages 368–368j, https://doi.org/10.1093/ije/dyx268[7]

Chapter 4: A Population Level Study of Peripartum Cardiomyopathy using the Rochester Epidemiology Project*

*Unpublished, incidents results reported in Douglass EJ, Blauwet LA, Cooper LT, Fairweather D. *A Population Level Study of Peripartum Cardiomyopathy using the Rochester Epidemiology Project*

Highlights

- Incidence peripartum cardiomyopathy in Olmsted County, MN 20.3/100,000 live births
- Infection, migraine, allergy and mental health diagnoses identified as novel risk factors
- All patients with follow-up available (93%) recovered heart function (LVEF ≥45%)
- No cardiac devices, transplants, mechanical circulatory support or deaths
- Nine cases had 15 subsequent pregnancies, 4 cases relapsed but fully recovered

Abstract

Objective: To estimate at the population level the incidence, clinical characteristics, presentation and outcomes of women with peripartum cardiomyopathy (PPCM) in a well-defined geographical region of the United States.

Methods: A retrospective cohort study using the Rochester Epidemiology Project was conducted to identify all incident cases of PPCM occurring in residents of Olmsted County, Minnesota between January 1, 1970 and December 31, 2014. Demographics, clinical information, disease characteristics and outcome data were obtained by individual medical record review.

Results: A total of 15 PPCM cases were identified and confirmed. The incidence of PPCM in Olmsted County, Minnesota during the time of the study was 20.3 per 100,000 live births. All cases recovered cardiac function to a left ventricular ejection fraction of ≥50%. There was a 26% rate of recurrent PPCM in subsequent pregnancies, but all recovered cardiac function. No index or subsequent pregnancy was complicated by ventricular assist device implantation, transplant or death.

Conclusions: PPCM occurred in approximately 20.3 per 100,000 live births in Olmsted County, Minnesota. A history of infections, migraines, allergies and mental health diagnoses were identified as potential novel risk factors.

Keywords: left ventricular ejection fraction, incidence, PPCM, race

Abbreviations

ACE, angiotensin converting enzyme

BMI, body mass index

BPM, beats per minute

ECHO, echocardiogram

GBS, group B strep

GED, general educational development or general education diploma

HDP, hypertensive disorders of pregnancy or hypertensive diseases of pregnancy

LA, left atrial

LV, left ventricle/ventricular

LVEF, LV ejection fraction

LVEDD, LV end diastolic diameter

LVESD, LV end systolic diameter

MDMA, 3,4-methylenedioxy-methamphetamine

mmHg, millimeters of mercury

OCD, obsessive compulsive disorder

PPCM, peripartum cardiomyopathy

PTSD, post-traumatic stress disorder

REDCap, Research Electronic Data Capture

REP, Rochester Epidemiology Project

RV, right ventricle

VAD, ventricular assist device

Introduction

Peripartum cardiomyopathy (PPCM) is a potentially life-threatening form of cardiac failure that strikes women with no history of heart disease in the last month of pregnancy or within 5 months of delivery[1,2]. PPCM is characterized by left ventricular (LV) systolic dysfunction, with LV ejection fraction (LVEF) confirmed by echocardiography as ≤45%,[3] leading to heart failure symptoms. Patients with PPCM can experience complete recovery of heart function.[4,5] Early diagnosis and treatment decrease mortality and increase the potential for full recovery of LV function. However, timely diagnosis is challenging, as the symptoms of PPCM are similar to the physiological changes that occur with normal pregnancy.[6,7]

Incidence estimates of PPCM vary widely between countries and within the United States from 25 per 100,000 live births in the United States[8] to 333 per 100,000 live births in Haiti.[9] Within the United States, rates vary from 25 per 100,000 live births in southern California to 185 per 100,000 live births in Augusta, Georgia.[7,8,10-14] The first population level estimate of PPCM incidence within the United States used the National Hospital Discharge Survey and reported 31 per 100,000 live births.[15] However, to our knowledge, a population level incidence study of PPCM that involved complete medical record review to confirm cases and abstract data has not previously been published. This study provides the first population level epidemiological study of incidence, clinical characteristics, presentation and outcomes of PPCM using complete medical record review available through the Rochester Epidemiology Project.

Methods

The project was approved by both the Mayo Clinic and Olmsted Medical Center Institutional Review Boards and conformed to the principles set forth in the Helsinki Declaration of 1975, as revised in 2013. All patients involved in the study provided written informed consent to allow the use of their medical records for research purposes as part of the Rochester Epidemiology Project (REP). Any patients who had not previously consented to participate in research through REP were excluded from the study.

The REP can be used to conduct population level epidemiologic research in Olmsted County, Minnesota, as previously described.[16] Briefly, the database links the medical record of most health care providers in the county including Mayo Clinic, Olmsted Medical Center and its affiliated hospital and a few private providers.[17] Together, these providers cover 90-96% of all health care to Olmsted County residents.[16] In Olmstead County, 98% of residents have agreed to participate in the REP.[18] The health care providers who participate in the REP use a unit (or dossier) medical record system where all medical data are assembled in one database.[17] The result is the linkage of medical records from essentially all sources of medical care available to, and utilized by, the Olmsted County population. These records therefore contain the details of every inpatient hospitalization, every outpatient visit to the offices, clinics or emergency rooms in the county, every physician visit to nursing homes or private homes, as well as every laboratory result, pathology report (including autopsies), imaging report and correspondence pertaining to individual patients. The medical details are collected by physicians providing subspecialty level medical care and are of high quality.

Data were collected for all Olmsted County, Minnesota residents diagnosed with PPCM from January 1, 1970 to December 31, 2014. Fifteen PPCM cases were identified from a list of 866 women 15 to 55 years of age living in Olmsted County, Minnesota from 1970-2014 with either a PPCM diagnosis code (ICD-9 674.5X, HICDA 4251610, 425310, BRK 0234X1) or a heart failure code (ICD-9 428.X, HIC 4270110, 4279133, BRK 23452). The case definition for PPCM was based on the criteria proposed by the National Heart, Lung and Blood Institute and the Office of Rare Diseases of the National Institutes of Health Workshop on Peripartum Cardiomyopathy[3] and included 1) development of cardiac failure in the last month of pregnancy or within 5 months of delivery, 2) absence of an identifiable cause for the cardiac failure, 3) absence of recognizable heart disease before the last month of pregnancy, and 4) LV systolic dysfunction demonstrated by classical echocardiographic criteria with a LVEF ≤45%.

Data of confirmed PPCM cases were individually abstracted from electronic and paper medical records available through the REP and entered into a Research Electronic Data Capture (REDCap) database.[19]

Data were analyzed using Microsoft Excel and StataIC 15.[20] Incidence was calculated for all female Olmsted County residents that were 15 to 55 years of age and considered to be at risk for PPCM. Annual birth rates for Olmsted County residents were obtained from the Minnesota Health Statistics Annual Summary Reports.[21,22] For primary diagnosis the outcomes of interest included cardiac assist device implantation, transplant and death. In addition, recurrence of disease was assessed, and the same outcomes of interest were measured as for primary diagnosis.

Results

From January 1970 to December 2014, 15 cases of PPCM were confirmed to have occurred in Olmsted County, Minnesota. Based on vital statistics data from the Minnesota Department of Health,[21,22] the incidence of PPCM from 1970 to 2014 in Olmsted County, Minnesota was determined to be 20.3 cases per 100,000 live births.[21,22]

Table 4.1 lists the demographic characteristics of the 15 PPCM cases from Olmsted County that were identified. The mean age was 29 (range, 17-39 years). Two thirds (66.7%, *n*=10) of the cases were white and 33.3% (*n*=5) black, with 4 of the 5 black women being recent immigrants from Africa (Table 4.1). There were no PPCM cases among women of Asian, Native American or Hispanic race/ethnicity. Seven of the cases (46.7 %) were overweight or obese prior to the index pregnancy (Table 4.1).

Socioeconomic factors varied widely among women in the study (Table 4.1). Eighty percent (*n*=12) of the women were married or living with a partner who was co-parenting with them, while 20% (*n*=3) were single parents. Education levels ranged from those who had not completed high school to those who had obtained graduate degrees. The women with the lowest level of education were African immigrants (data not shown). Sixty percent (*n=9*) of the cases had private insurance while 40% (*n*=6) were on medical assistance. Seven of the women (46.6%) had a history of tobacco use (current at diagnosis or past) and 53.3% (*n*=8) had a history of alcohol use. Only 1 woman had a history of illegal drug use (i.e., marijuana and 3,4-methylenedioxy-methamphetamine/MDMA).

Table 4.2 describes the medical history of the women from Olmsted County prior to their index pregnancy and diagnosis of PPCM. Only 1 woman had a history of hypertension. Three had a history arrhythmia with 1 case of tachycardia, 1 case of

tachycardia and palpitations, and 1 case of non-symptomatic supraventricular tachycardia. No further types of cardiovascular diseases were recorded. Mental health diseases were common (66.7%, *n*=10), with 60% (*n*=9) of the women diagnosed with depression, 20% (*n*=3) with anxiety, and 40% (*n*=6) having other mental health diagnoses. A history of migraine was found in 10 cases (66.7%), but none were taking migraine medications during their index pregnancy or at diagnosis of PPCM. Nine (60%) cases had a history of infectious diseases. Two cases had a history of unusual or specific exposure to chemicals during their lives, 1 to pesticides weekly as a child and the other to black mold as an adult. Eight cases (53.3%) had a history of allergies. Two women, both Caucasian, had past diagnoses of cancer. Both women had melanoma treated with surgical excision. No one in the cohort had been treated with chemotherapy agents or chest radiation. No cases had a history of diabetes.

Table 4.3 describes the obstetric and gynecological history (prior to the index pregnancy) of women with PPCM from Olmsted County. The majority of the women (73.3%, *n*=11) in the cohort were nulliparous, 2 (13.3%) primiparous and 2 (13.3%) multiparous, each with ≥4 previous live births. Of the 4 women with previous live births, 75% (*n*=3) had a history of some type of hypertensive disorder of pregnancy (HDP) during at least one of their previous pregnancies that carried to term, with some women diagnosed with more than one type of HDP in separate pregnancies. All three women with previous live births and history of a HDP were diagnosed with gestational hypertension. Two were also diagnosed with preeclampsia, and the third had an additional diagnosis of an unknown type of HDP.

Table 4.4 describes the characteristics of the index pregnancies of the 15 PPCM cases. Twelve (80%) women had singleton pregnancies and 3 (20%) had twin pregnancies. Eighteen infants were born to the cohort cases, with 13 (72.2%) of the offspring being female and 5 (27.8%) male. Seven (46.7%) of the 15 index PPCM cases in the study had emergency C-sections and 2 (13.3%) needed device assistance during vaginal delivery. The mean gestational age was 37 weeks (range 32-42 weeks) and the mean birthweight was 2,907 grams (range 1,635-4,760 grams). Seven (38.9%) of the 18 infants were classified as low birthweight (<2,500 grams) and there were 5 premature births (before the 37^{th} weeks of gestation). Breastfeeding rates in PPCM patients were initially 60% (*n*=9) and decreased to at least 40% (*n*=6) after diagnosis, but may have been even lower as breastfeeding status post diagnosis was missing for four cases. The majority of the women (86.7%, *n*=13) had access to standard medical care during their pregnancy. Two thirds (66.7%, *n*=10) of the women had a diagnosis of some type of HDP, with the most common diagnosis (46.7%, *n*=7) being preeclampsia. In addition, 6 (40%) women were placed on bedrest during their index pregnancy, 1 (7%) had gestational diabetes, 1 (7%) was treated with tocolytic therapy, and 10 (66.7%) completed at least one course of antibiotics during pregnancy, with 3 (20%) women prescribed 4 or more courses of antibiotics.

Table 4.5 presents characteristics including physical exams at diagnosis, echocardiogram results, treatments and outcomes for the 15 women with PPCM. Thirteen (86.7%) women presented with significantly elevated blood pressure (data not shown). Symptoms of heart failure (i.e., rales, wheezing, pulmonary edema, peripheral edema, jugular venous distention, and/or ascites) were present in 13 (86.7%) women, left heart failure only in 3 (20%), right heart failure only in 3 (20%), and symptoms of both right and

left sided heart failure in 7 (46.7%) women (data not shown). At diagnosis, the mean LVEF was 35% (range 20-45%) and the mean LV end diastolic diameter (LVEDD) was 5.5 cm (range 4.0-6.4 cm).

Figure 4.1 shows the trends in LVEF over the first 5 years of the study period for the 15 PPCM cases, although some women had data available up to 14 years post diagnosis. The 14 women with follow-up echocardiography data available all recovered (LVEF ≥50%) with 13 recovering by year 4. Timing of recovery ranged widely: 7 (46.6%) women recovered by 6.5 months, 2 (13.3%) recovered between 1 and 2 years, and 4 (26.6%) recovered by 4 years. Timing of recovery for the remaining patient is unknown, as she had no follow-up echocardiogram until year 12, at which point she had recovered (Table 4.5, Figure 4.2). All 15 patients in this cohort were treated with guideline directed medical therapy for heart failure, with the most common medications being angiotensin converting enzyme (ACE) inhibitors (93.3%, *n*=14), diuretics (80%, *n*=12) and beta blockers (73.3%, *n*=11) (Table 5). No pacemakers or internal cardiac defibrillators were implanted, no patients underwent ventricular assist device implantation or transplantation, and there were no deaths in this cohort during a mean follow up time of 13.7 years (Table 4.5, Figure 4.2). Post diagnosis, 6 (50%) of the 12 women for whom contraception records were available underwent sterilization after receiving counseling by medical providers regarding the risk of PPCM relapse during subsequent pregnancy. The sterilizations occurred at various time points including 1 at index delivery, 1 shortly after diagnosis, 3 at subsequent pregnancy (each after termination of that pregnancy), and 2 after subsequent delivery.

Table 4.6 summarizes the data on subsequent pregnancies in this cohort. Nine (60%) women had a total of 15 subsequent pregnancies, and 2 (13.3%) women may have

had further subsequent pregnancies after they were lost to follow-up. Of the 15 subsequent pregnancies, 7 (46.6%) resulted in live birth, 3 (20%) in spontaneous abortion and 5 (33.3%) were terminated. The relapse rate in this cohort was (26.7%) but all 4 women who relapsed recovered their LV function post relapse (Table 4.6 and Figure 4.2).

Discussion

The estimate of the incidence of PPCM in Olmstead County from 1970-2014 was 20.3 per 100,000 live births, which is lower than previous estimates of 25 to 185 per 100,000 live births. [7-9,11,15,23] Our findings may reflect a more accurate population level incidence estimate for several reasons. All PPCM cases in a defined geographical area were confirmed using REP data instead of relying on diagnosis codes. Although 58 women had a diagnosis code for PPCM in their medical record, after record review, only 15 (26%) met the diagnostic criteria for PPCM.[3] Thus, previously published epidemiologic studies of PPCM may have overestimated the disease incidence by including women who had the diagnosis code for PPCM in their medical record but did not actually meet diagnostic criteria for PPCM.

Previous studies of PPCM reported that black women have the highest rate of PPCM followed by white women, while Hispanics and Asians have the lowest rate.[7-9,11,15,23] Similar race/ethnicity patterns were observed in this study (Table 4.1). Differences in demographics may have led to a lower overall incidence of PPCM in this study compared with previous studies.[24] Olmsted County is, in general, less racially diverse than some other regions of the US. Based on the 2010 US Census, the US population was 76.6% white and

13.4% Black or African American whereas Olmsted County was 84.7% white and 6.1% Black or African American.[24,25] Based on these Census numbers the incidence of PPCM was higher than expected in Blacks and lower than expected in all other racial groups.

The women in this study were evenly divided above and below 30 years of age, differing from previous studies where PPCM was associated with increased maternal age, reporting that over half of the cases occurred in women >30 years of age.[8,10,11,15] The majority of women in our study were nulliparous, which differs from previous studies that reported multi-parity as a risk factor for PPCM.[7,10-14] Similar to previous studies,[26] there was an increased rate (20%) of multifetal gestations among women diagnosed with PPCM in our cohort, compared with 2.1-3.5% births nationwide.[27]

Hypertensive disease of pregnancy, especially preeclampsia, is known to be a risk factor for the development of PPCM.[26,28,29] The cohort in this study had high rates of HDP during the index pregnancy, with the most common diagnosis being preeclampsia. Seven of the 15 women with PPCM (46.6%) had preeclampsia (Table 4.4), a rate that is almost 12x greater than the national prevalence of 4%.[30] Thus, this study provides support for the hypothesis that preeclampsia and PPCM may have an overlapping pathophysiology with an anti-angiogenic milieu and inflammation linking the conditions.[26,31-34] Research is needed to investigate this possibility.

This study identified some possible novel risk factors for PPCM including one or more mental health diagnoses (primarily depression and anxiety), migraine and allergies (Table 4.2). Of note, migraine, depression, anxiety and allergies occur more often in women than men in the general population and mast cell activation and inflammation play a role in promoting migraine and allergic reactions.[35-38] In this study, high rates of antibiotic

use during pregnancy (Table 4.4) suggest that viral/bacterial infection may play a role in the pathogenesis of PPCM. Several investigators have postulated that myocarditis, which is primarily caused by viral infections but also by bacterial infections, could cause PPCM.[39-42] However, myocarditis occurs more often in men than women (3.5:1 men to women).[43-45] Other possible risk factors for PPCM identified in this cohort include being a current or past smoker and alcohol use (Table 4.2).

Another interesting and potential novel finding in this study was that of the 18 infants born to the PPCM cases, 72.2% (*n*=13) were female and only 27.8% (*n*=5) were male. In Olmsted County, the average birth rate by sex during the years of the study were 51% male and 49% female [21,22]. Thus, the percentage of female neonates born to women diagnosed with PPCM appears to be higher than expected. A recent study showed a similar trend towards higher numbers of female sex in the offspring of women diagnosed with PPCM both in the index pregnancy (59% female) and in the subsequent pregnancies (63% female).[46] Other studies have shown mixed results. [7,47-49] To our knowledge the role of fetal sex in the pathogenesis of PPCM has not been investigated. However, a recent study found that women carrying female fetuses had greater inflammatory responses after immune challenge compared to women carrying male fetuses. Results from other studies suggest that fetal sex may also play a role in maternal physiology during pregnancy including blood pressure.[50-52] Overall, these findings suggest that fetal sex may play a role in the pathogenesis of PPCM and should be further investigated.

Medical guidelines state that women with a diagnosis of PPCM should be counseled to avoid future pregnancies due to concern that the mother may develop heart failure relapse.[4,53] However, all women in this study who had follow-up echocardiograms

available regained normal cardiac function with time (Table 4.5 and Figure 4.1). While past studies reported adverse outcomes in women with PPCM who pursue subsequent pregnancy including the need for cardiac devices, mechanical support, transplantation and death,[11,15,54-59] none of these poor outcomes were observed in this cohort (Table 4.5, Table 4.6, and Figure 4.2). The results from this study suggest that women diagnosed with PPCM that obtain special cardiac monitoring can have safe subsequent pregnancies.

Using diagnosis codes to identify cases has limitations and can lead to over or under estimation of cases. This study screened all women living in the study area whose medical records included the diagnoses codes for heart failure in an attempt to identify cases that were miscoded. But no additional cases were found. A major strength of the study was the use of the REP to create a population level cohort from a specific geographical region isolated from other large medical centers with almost complete availability of medical records for the study. Importantly, only 26% of women who had a diagnosis code of PPCM in their medical record met the case definition. We were not able to screen all women who had pregnancies due to the large sample size. It is also possible that cases may have been missed as medical professionals were not as aware of PPCM in the past; however, by screening all women diagnosed with heart failure we minimized this possibility. A strength of the study was the ability to individually examine all medical records of potential cases without relying on diagnosis codes for inclusion of cases so that only confirmed cases were included in the study. Due to the methodology of the study, it is possible a few very mild cases may have been missed, but all women miscoded for PPCM were excluded from the study making our incidence calculation more accurate than studies that did not use medical records to confirm cases. Other inherent limitations included the small sample size, the

lack of racial/ethnic diversity in Olmsted County, and the retrospective cohort design that limited data to what was available in the medical record.

Conclusion

A population level epidemiological study of PPCM in Olmsted County, Minnesota found 20.3 cases per 100,000 live births. Women with PPCM had complete cardiac recovery and multiple subsequent pregnancies with no enduring cardiac dysfunction despite a 26% relapse rate. We identified potential novel risk factors for PPCM including depression, anxiety, infections, migraine and allergies. These potential risk factors should be validated using larger cohorts.

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Table 4.1 Maternal characteristics (*n*=15)

Characteristic	Value
Age (y)	29 (17-39)
Pre-pregnancy BMI (kg/m^2)*	
< 18.5	0 (0.0)
18.5-24.9	7 (46.7)
25.0-29.9	2 (13.3)
≥ 30	5 (33.3)
Race/Ethnicity	
White	10 (66.7)
Black	5 (33.3)
African American	1(6.7)
African Immigrant	4 (26.6)
Hispanic	0 (0.0)
Marital Status	
Single	3 (20.0)
Married	8 (53.3)
Domestic Partner	4 (26.7)
Education	
< High school	2 (13.3)
High school or GED	3 (20.0)
Some college or associate degree	5 (33.3)
≥ College degree	5 (33.3)
Health Insurance	
Private	9 (60.0)
Medical assistance	6 (40.0)
Smoking	
At diagnosis	2 (13.3)
Before pregnancy	5 (33.3)
Never	8 (53.3)
Alcohol Use*	
At diagnosis	2 (13.3)
Before pregnancy	6 (40.0)
Never	6 (40.0)
Drug Use	
Current	0 (0.0)
Past	1 (6.7)
Never	14 (93.3)

Abbreviations: BMI, body mass index; GED, general educational development or general education diploma

Data are n (%) or mean (range) unless otherwise specified.

*One unknown.

Table 4.2 Maternal medical history (*n*=15)

Patient	Medical history
1	**Past smoker**, **current alcohol use***, **depression**, post-partum depression, adjustment disorder, 2 attempted suicides, alcohol abuse, >5 infections (mumps, trichomonas, genital herpes simplex II, *Molluscum contagiosum*, condylomata, chorioamnionitis)
2	**Past alcohol** use, **migraine**
3	**Past smoker**, **past alcohol use**, **depression**, oppositional disorder, dysthymia, 1 environmental allergy, 1 infection (herpes simplex), **migraine**, environmental exposure (repetitive pesticide exposure as a child)
4	**Past smoker**, **past alcohol use**, obesity, melanoma - no chemotherapy, adjustment disorder with mixed **emotional** features, 1 drug allergy
5	**Current smoker**, **past alcohol use**, **depression**, 2 drug allergies, >5 infections (pyelonephritis, frequent and recurrent bladder infections), **migraine**
6	**Past smoker**, unknown alcohol use, obesity, **depression**, anxiety, asthma, 1 drug allergy, 1 infection (appendicitis), **migraine**
7	**Current smoker**, **current alcohol use**, past drug use, obesity, **depression**, adjustment disorder with mixed disturbance of emotions and conduct, parent-child problems, PTSD, alcohol abuse, dysthymic disorder, borderline personality traits, 1 environmental allergy, >5 infections (gonorrhea, chlamydia x2, recurrent urinary tract infections, bacterial vaginosis)
8	**Past smoker**, **migraine**
9	Obesity, tachycardia, palpitations, **depression**, anxiety, OCD, panic attacks, panic disorder with agoraphobia, dysthymia, asthma, multiple allergies (drugs, food, environmental, other), 1 infection (recurrent cystitis), **migraine**
10	Overweight, arrhythmia, tachycardia, **depression**, anxiety, PTSD, 5 infections (GBS, herpes labials, hepatitis A, hepatitis B, latent tuberculosis)
11	Overweight, 3 infections (hepatitis B, malaria, infection of unknown type)
12	**Past alcohol use**, obesity, hypertension, melanoma - no chemotherapy, 3 drug allergies, **migraine**
13	Supraventricular tachycardia, **migraine**
14	**Depression**, asthma, **migraine**
15	**Past alcohol use**, **depression**, multiple allergies (food, drug, environmental, other), 2 infections (scarlet fever, recurrent otitis media), **migraine**, fibromyalgia, chronic fatigue syndrome, environmental exposure (black mold)

Abbreviations: OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder; GBS, group B strep

*Of the 15 women in this study 10 (66.7%) had a history of current or past smoking and/or alcohol use, 10 (66.7%) a history of migraines, 9 (60.0%) had past infections, 10 (66.7%) had a history of mental health diagnoses, and 8 (53.3%) had allergies.

Table 4.3. Obstetric history prior to index pregnancy (*n*=15)

Obstetric history	**Value**
Live Births	
0	11 (73.3)
1	2 (13.3)
2-3	0 (0.0)
4-5	1 (6.7)
>5	1 (6.7)
Multifetal gestations	0 (0.0)
Hypertensive disease of pregnancy	3 (20.0)
Chronic hypertension	0 (0.0)
Pre-eclampsia	2 (13.3)
Gestational hypertension	3 (20.0)
Unknown type	1 (6.7)
Gestational Diabetes	0 (0.0)

Data are n (%).

Table 4.4 Index pregnancy obstetrics and neonatal characteristics (*n*=15)

Characteristic	Value
Assisted reproduction	2 (13.3)
Access to standard medical care during pregnancy	13 (86.7)
Hypertensive disease of pregnancy	10 (66.7)
Chronic hypertension	0 (0.0)
Gestational hypertension	3 (20.0)
Preeclampsia*	7 (46.7)
Eclampsia	0 (0.0)
Pre-eclampsia superimposed on chronic hypertension	1 (6.7)
Unspecified	1 (6.7)
Gestational diabetes	1 (6.7)
Antibiotic use during pregnancy	10 (66.7)
Bed rest	6 (40.0)
Tocolytic therapy	1 (6.7)
Method of delivery	
Spontaneous vaginal	4 (26.7)
Assisted vaginal	2 (13.3)
Planned Cesarean section	2 (13.3)
Emergency Cesarean section	7 (46.7)
Number of neonates	
Single	12 (80.0)
Twins	3 (20.0)
Neonate sex	
Male	5 (27.8)
Female	13 (72.2)
Breastfeeding	
At delivery	
Yes	9 (60.0)
Unknown	1 (6.7)
After diagnosis	
Yes	2 (13.3)
Unknown	4 (26.7)
Gestational age (wks) †	37 (32-42)
Premature (<37 weeks)	5 (35.7)
Birthweight (g)†	2,907 (1,635 – 4,760)
Low birth weight (<2,500 g)	7 (38.9)

Data are n (%) or mean (range) unless otherwise specified.

*Two cases had diagnoses of both gestational hypertension and preeclampsia and are counted in both of these categories.

†1 missing

Table 4.5. Index pregnancy maternal cardiovascular characteristics (*n*=15)

Characteristic	Value
Clinical Features	
Blood pressure	
Systolic (mmHg)	145 (114-180)
Diastolic (mmHg)	94 (56-120)
Heart rate (bpm)	99 (70-150)
Murmur	7 (46.7)
Signs suggestive of left heart failure[*,†]	9 (60.0)
Signs suggestive of right heart failure[‡,§]	9 (60.0)
Echocardiograph Parameters	
LVEF (%)	35 (20 - 45)
LVEDD (cm)	5.5 (4.0 - 6.4)
LVESD (cm)	4.3 (3.1 – 5.6)
Ventricular septal wall thickness (cm)	1.0 (0.8 – 1.2)
Posterior wall thickness (cm)	0.9 (0.8 – 1.2)
RV enlargement	1 (6.7)
RV hypokinesis	3 (20.0)
LA volume index (mL/m^2)	33 (15 – 70)
Valvular heart disease[·§·‖]	7 (46.7)
Pericardial effusion	9 (60.0)
Treatment	
Medication	15 (100)
ACE inhibitor	14 (93.3)
Angiotensin II receptor blocker	1 (6.7)
Beta blocker	11 (73.3)
Diuretic	12 (80.0)
Anticoagulant	6 (40.0)
Bromocriptine	0 (0.0)
Vasodilator	3 (20.0)
Antiarrhythmic	3 (20.0)
Calcium channel blocker	2 (13.3)
Nitroglycerin	1 (6.7)
Potassium	2 (13.3)
Magnesium sulfate	1 (6.7)
Mechanical circulatory support	0 (0.0)
Cardiac device implantation	0 (0.0)
VAD	0 (0.0)
Transplant	0 (0.0)
Death	0 (0.0)
Left ventricular recovery[†]	14 (93.3)
Sterilization	6 (40.0)

Abbreviations: mmHg, millimeters mercury; bpm, beats per minute; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular

end systolic diameter; RV, right ventricle; LA, left atrial; ACE, angiotensin-converting enzyme; VAD, ventricular assist device.
Data are n (%) or mean (range) unless otherwise specified.
[*]Rales, wheezing, pulmonary edema.
[†]1 missing.
[‡] Jugular venous distension, ascites, peripheral edema.
[§]2 missing.
[‖] Designation of valvular heart disease was based on echocardiogram interpretations and included disease categorized as mild/moderate, moderate, moderate/severe, or severe. Valvular disease involved the mitral and or tricuspid valves in all 7 patients. One patient additionally had disease in the pulmonary valve as well as a thickened mitral valve.

Table 4.6 Obstetric and cardiac outcomes of subsequent pregnancy (*n*=9)

Outcomes	Value
Pregnancy outcome (*n*=15)*	
Delivered	7 (46.7)
Spontaneous abortion	3 (20.0)
Terminated	5 (33.3)
Maternal outcome	
Relapse (*n*=4)	4 (26.7)
Recovery after relapse (*n*=4)	4 (100)

Data are n (%).

*Nine women had a total of 15 subsequent pregnancies. Six of these women had 1 subsequent pregnancy each, one woman had 4, one had 3, and one had 2.

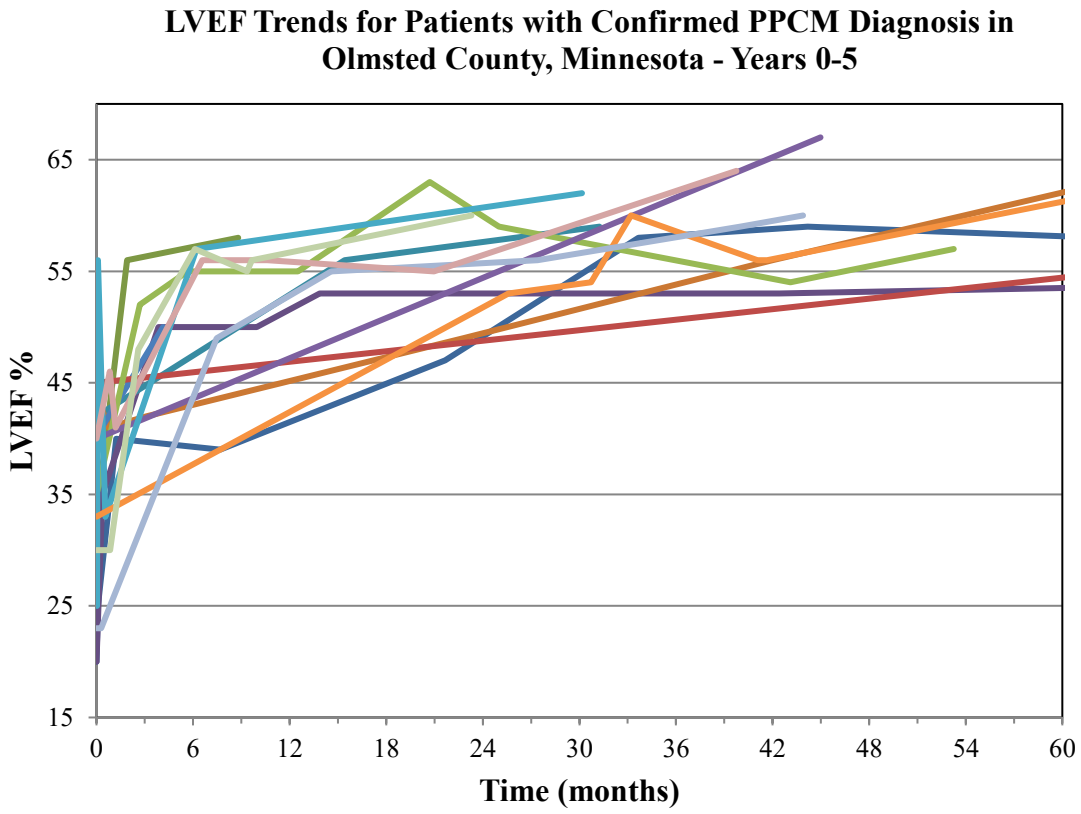

Figure 4.1 Trends in LVEF for confirmed cases of PPCM for the first 5 years post diagnosis.

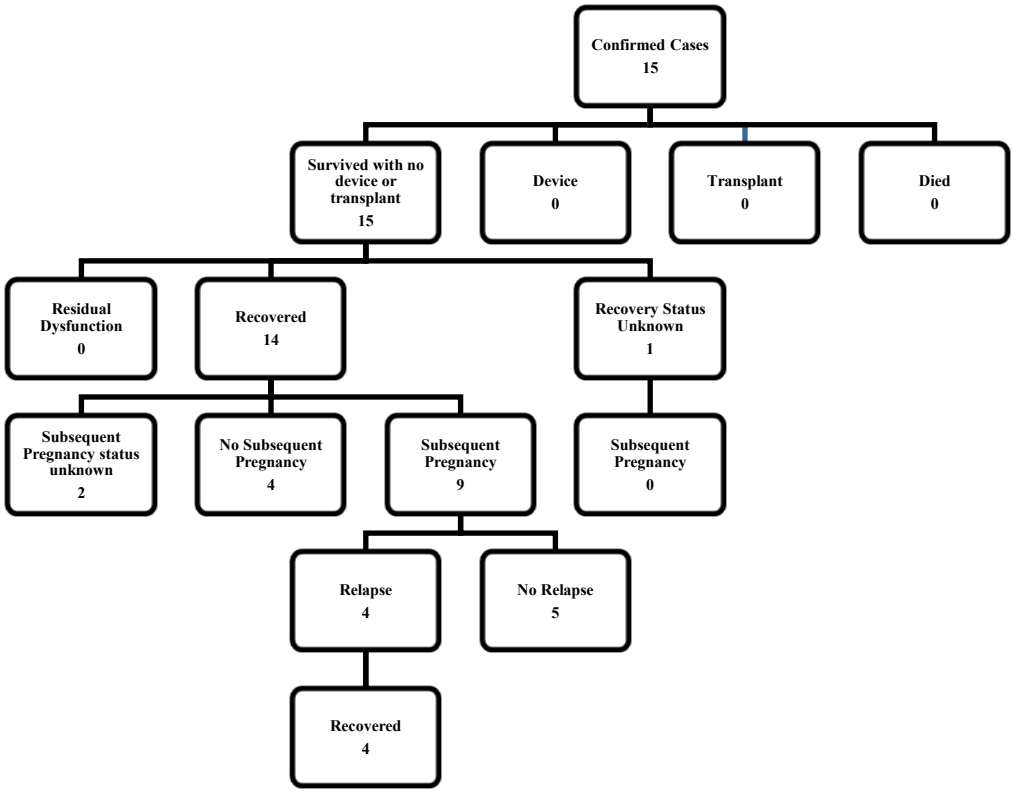

Figure 4.2 Outcomes of the 15 patients with PPCM

14/15 of the patients that had follow-up echocardiography data available recovered. There were no cardiac device implantations, transplants or deaths in this cohort. Nine of the 14 recovered women had subsequent pregnancies. Four of the 9 relapsed, but all recovered.

Chapter 5: A Case-Control Study of Peripartum Cardiomyopathy Using the Rochester Epidemiology Project*

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Abstract

Background: The incidence of peripartum cardiomyopathy (PPCM) is known through referral center databases that may be affected by referral, misclassification, and other biases. We sought to determine the community-based incidence and natural history of PPCM using the Rochester Epidemiology Project.

Methods and Results: Incident cases of PPCM occurring between January 1, 1970, and December 31, 2014, were identified in Olmsted County, Minnesota. A total of 15 PPCM cases were confirmed yielding an incidence of 20.3 cases per 100,000 live births in Olmsted County, Minnesota. Clinical information, dis- ease characteristics, and outcomes were extracted from medical records in a 27-county region of the Rochester Epidemiology Project including Olmsted County and matched in a 1:2 ratio with pregnant women without PPCM. A total of 48 women were identified with PPCM in the expanded 27-county region. There was 1 death and no transplants over a median of 7.3 years of follow-up. Six of the 23 women with subsequent pregnancies developed recurrent PPCM, all of whom recovered. Migraine and anxiety were identified as novel possible risk factors for PPCM.

Conclusions: The population-based incidence of PPCM was 20.3 cases per 100,000 live births in Olmsted County, Minnesota. Cardiovascular outcomes were generally excellent in this community cohort.

Key Words: Heart failure, incidence, migraine, pregnancy.

Introduction

Peripartum cardiomyopathy (PPCM) is defined as the development of cardiac failure in the last month of pregnancy or within 5 months of delivery in women with no history of heart disease and no other identifiable cause for cardiac failure. PPCM is characterized by left ventricular (LV) systolic dysfunction with an LV ejection fraction (LVEF) of 45% and confirmed by echocardiography,[1] as well as heart failure symptoms. Women with PPCM can experience complete recovery of heart function[2,3] with early diagnosis and treatment. Timely diagnosis is challenging because the symptoms of PPCM are similar to the physio- logical changes that occur during normal pregnancy and postpartum.[4,5]

The incidence estimates of PPCM vary widely between countries and within the United States from 25 cases per 100,000 live births in the United States[6] to 333 per 100,000 live births in Haiti.[7] Within the United States, rates vary from 25 cases per 100,000 live births in southern California to 185 per 100,000 live births in Georgia.[5,6,8-13] The first population-level estimate of PPCM incidence in the United States used the National Hospital Discharge Survey, relying on *International Classification of Diseases* (ICD) codes to confirm the diagnosis, and reported 31 cases per 100,000 live births.[13] A population-level study of PPCM with a complete medical record review for data abstraction has not been published previously. This study provides the first population-level epidemiologic study describing the incidence and outcomes of PPCM using a comprehensive medical record review through the Rochester Epidemiology Project (REP) using a case-control design to examine demographic and clinical characteristics, presentation, potential risk factors, and outcomes.

Methods

Participants

This project was approved by both the Mayo Clinic and Olmsted Medical Center Institutional Review Boards and conformed to the principles set forth in the Declaration of Helsinki 1975, as revised in 2013. All patients involved in the study provided written informed consent to allow the use of their medical records for research purposes as part of the REP. Patients who had not previously consented to participate in research through the REP were excluded from the study.

Source of Data

The REP has been used to conduct population-level epidemiologic research in Olmsted County, Minnesota, as described previously.[14] Briefly, the database links the medical record of most health care providers in the county, including Mayo Clinic and Olmsted Medical Center and their affiliated hospitals as well as a few private providers who provide 90% 96% of all health care to Olmsted County residents.[14-16] Data for this study was available from 3 regions: Olmsted County (1 county), a 7-country region that included Olmsted County and 6 other surrounding counties, and a 27-county region that incorporated the 7 counties as well as other counties in southern Minnesota and western Wisconsin.[17] Olmsted County has a coverage rate of 99.9% from January 1, 1970, through December 31, 2014, and the 7-county region has a 93.8% coverage rate from January 1, 1976, through December 31, 2014. Starting January 1, 2010, the REP was expanded to include a total of 27 counties.[14-17] The 27-county region uses the same data linkage system as the REP and has an overall coverage rate of 60.9% from January 1, 2010, to December

13, 2014.[14-17] The lower coverage rate is due predominantly to not all heath care facilities within the region collaborating in the REP.[17] The REP has electronic indexes that include demographic information, diagnostic and procedure codes, health services use data, outpatient drug prescriptions, laboratory test results, imaging and procedure reports, and information about smoking, height, weight, and body mass index.[14-17] The demographic, racial, ethnic, and socioeconomic make- up of the 27 county region REP has been shown to be representative of the Minnesota/Wisconsin area and to a large segment of the US population.[17]

Study Population

Data were collected for all Olmsted County, Minnesota residents diagnosed with PPCM from January 1, 1970, through December 31, 2014. PPCM cases from the 1-county region were broadly identified from a list of 866 women 15 55 years of age living in Olmsted County, Minnesota, from 1970 to 2014 with a PPCM diagnosis code (ICD-9 674.5X, Hospital International Classification of Disease Adaptation [HICDA] 4251610, 4251310, BRK 0234 1) or a heart failure code (ICD-9 428.X, HIC 4270110, 4279133, BRK 23452); codes that were used for these dis- ease classifications during this time period. The older HICDA code was used to identify PPCM cases during the years before the use of ICD-9 diagnosis codes. From the original 866 patients identified with possible PPCM, 15 cases were confirmed as PPCM. Population-level data were only available for Olmsted County, so the incidence of PPCM was based on Olmsted County data.

To increase the sample size of the study, data were also collected from January 1, 1976, through December 31, 2014, by individual record review for the 7-county and the

27-county regions. Because heart failure diagnosis codes had not yielded any additional cases of PPCM in the survey of 866 records in Olmsted County, only diagnosis codes for PPCM (ICD-9 674.5X) or cardiomyopathy (HICDA 4250310) were used for the expanded regions. From the 7- county region, we identified an additional 242 women with PPCM diagnoses, and a further 69 patients from the 27- county region with PPCM diagnoses. From these potential cases, medical record review confirmed 33 additional cases of PPCM, which combined with the 15 cases from Olmsted County, provided a total of 48 cases for the study (Fig. 5.1).

In total, 1177 potential cases of PPCM were individually screened from all 3 regions using a case definition for PPCM based on the criteria proposed by the National Heart, Lung and Blood Institute and the Office of Rare Diseases of the National Institutes of Health Workshop on Peripartum Cardiomyopathy[1] that included (1) the development of cardiac failure in the last month of pregnancy or within 5 months of delivery, (2) an absence of an identifiable cause for the cardiac failure, (3) an absence of recognizable heart disease before the last month of pregnancy, and (4) a LV systolic dysfunction demonstrated by classical echocardiographic criteria with an EF of 45% (Fig. 5.1).

Control patients were selected from a pool of 52,682 women 15 55 years of age who lived and gave birth within the 27-county region of the REP from January 1, 1970, through December 31, 2014. Controls were matched on a 2:1 basis by age, race, and number of babies born during the index pregnancy (index pregnancy refers to the pregnancy related to initial PPCM diagnosis for cases and the matched pregnancy in each control).

Data Collection

Data regarding demographics, medical history, index pregnancy, and outcomes for the 48 confirmed PPCM cases and the 96 selected controls were abstracted from electronic and paper medical records available through the REP and entered into a Research Electronic Data Capture (REDCap) database.[18]

Statistical Analysis

The incidence was calculated for all Olmsted County female residents who were 15-55 years of age and considered to be at risk for PPCM. Annual birth rates for Olmsted County residents were obtained from the Minnesota Health Statistics Annual Summary Reports.[19,20] To compare cases and controls, the Student's *t* test or Wilcoxon Mann Whitney test were used to assess differences for continuous variables with normal or skewed distribution, respectively. The Fisher exact test or the x^2 test were used to evaluate categorical variables. A *P* value of <.05 was considered statistically significant. Categorical data are presented as frequency (*n*) and percent (%) and numeric data as mean standard deviation for normally distributed data and median (interquartile range) for non-normally distributed data, unless otherwise specified. Missing data were excluded from the analyses. Column total percentages are based on excluding missing data. Data were analyzed using Stata/IC 15.[21]

Results

Fifteen women in the single county area of Olmsted County, Minnesota, who met the definition for a diagnosis of PPCM were identified. Based on vital statistics data from

the Minnesota Department of Health,[19,20] the incidence of PPCM from 1970 through 2014 in Olmsted County, Minnesota, was determined to be 20.3 cases per 100,000 live births.

An additional 33 women who lived in the larger 27 county REP area and met the criteria for a diagnosis of PPCM were identified that, when added to the 15 cases from Olmsted County, provided the 48 overall number of cases for the case control study (Fig. 5.1). Ninety-six women were identified as controls with a 2:1 matching based on age, race, and number of infants born during the index pregnancy. Demographics of cases and controls are listed in Table 5.1. The mean age of the cohort was 28 years (range15-44 years) (Table 5.1). The cohort was 79.2% White, 18.7% Black (a mix of African American [6.2%] and African immigrants [12.5%]) and 1 woman (2.1%) who identified as both Native American and Hispanic. Women in the PPCM cohort had a higher median body mass index than women in the control cohort (25.2 kg/m^{2}vs 23.6 kg/m^2, P = .01), were more likely to be overweight or obese (66.7% vs 41.7%, P = .005), and were more likely to have government-sponsored health insurance (i.e. Medicaid), whereas women in the control cohort were more likely to have private health insurance (53.3% vs 25.6%, P = .001) (Table 5.1). There were no statistically significant differences in marital status, education level, smoking status, and his-tory of hypertension (8.3% vs 2.1%, P = .01), anxiety (25.0% vs 10.4%, P = .03) and migraine (43.8% vs 15.6%, P< .001) compared with controls (Table 5.2). There were no differences observed in hyperlipidemia, heart disease, cancer, depression, asthma, allergies, infections, diabetes, or chemical exposure between the 2 groups (Table 5.2). Among the women for whom these data were available, women diagnosed with PPCM were more likely to have a history of hypertensive disorders of pregnancy (HDP), predominantly gestational hypertension and preeclampsia (40.0% vs

4.2%, *P* = .02), and a higher likelihood of gestational diabetes (4.8% vs 3.1%, *P* = .04) in previous pregnancies (Table 5.3).

Index pregnancy characteristics are listed in Table 5.4 Women in the PPCM cohort were more likely to have been diagnosed with HDP (56.3% vs 12.5%, *P* < .001) and more likely to have been placed on bed rest (28.2% vs 12.6%, *P* = .03) during their index pregnancy compared with women in the control group. The index pregnancies of women diagnosed with PPCM were less likely to have been planned pregnancies than those of controls (32.4% vs 54.4%, *P* = .03). Women in the PPCM cohort were also significantly more likely to have had an emergency cesarean section than women in the control cohort (43.8% vs 14.6%, *P* < .001). Women in the PPCM cohort were more likely to have had a cardiac indication for cesarean section than women in the control cohort (55.1% vs 7.1%, *P* = .01) (Table 5.4). Infants born to women in the PPCM cohort had a lower median gestational age (37 weeks vs 39 weeks, *P* = .004), were significantly more likely to be born prematurely (< 37 weeks gestation) (43.8% vs 22.9%, *P* = .003), had a significantly lower median birth weight (2445 g vs 3190 g, *P*= .01) and were more likely to be born at a low birth weight (<2500g) (45.8% vs 24.8%, *P* = .01). Women in the PPCM cohort seemed to be less likely to breastfeed, but this difference did not reach statistical significance(59.9% vs 75.8%, *P* = .06). However, the rates of breast- feeding in the PPCM cohort decreased significantly after diagnosis (59.9% vs 24.3%, *P* = .009) (Table 5.4).

Table 5.5 presents characteristics, including physical examination at diagnosis, echocardiography findings, and treatments and outcomes for the 48 cases in our cohort. Eleven of the women (22.9%) were diagnosed with PPCM during pregnancy and the other 37 (77.1%) were diagnosed postpartum, with the median time of diagnosis being 4 days

postpartum (Table 5.5). The majority of cases (41/48, 85.4%) presented with elevated blood pressure[22] and/or heart failure symptoms (44/48, 91.7%) with 1 patient missing information on symptoms at diagnosis. Indications for cardiac screening in the 3 cases without heart failure symptoms included arrhythmias and a new heart murmur. The median LVEF at diagnosis was 34% (range 12% 45%) and the median LV end diastolic diameter was 5.7 cm (range 4.0 7.4 cm). Forty-seven of the women (97.9%) were treated with medications, the most common being angiotensin-converting enzyme inhibitors (87.5%, *n* = 42), diuretics (87.5%, *n* = 42), and beta-blockers (79.2%, *n* = 38) (Table 5.5). One patient had an intra-aortic balloon pump placed and subsequently died (Table 5.5, Fig. 5.1). This death was the only one in the cohort. No pacemakers or internal cardiac defibrillators were implanted and no patients under- went LV assist device implantation or transplantation during a median follow up time of 7.3 years (range 0.3 27.8 years) (Table 5.5, Fig. 5.1).

Supplementary Fig. 1 shows the trends in LVEF of the confirmed cases over the first 5 years of the study. Forty- three of the women (89.6%) diagnosed with PPCM 2: recovered cardiac function (LVEF 50% per follow-up echocardiography) (Table 5.5, Fig. 5.1). The timing of the recovery ranged from 3 days to just >12 years, with the median time to recovery approximately 4.5 months (Table 5.5). Two women had residual cardiac dysfunction and no follow-up echocardiograms were recorded for 2 additional women in the PPCM cohort, so recovery status could not be determined (Fig. 5.1).

Among the control cohort of 96 women, 56 (62.6%) had a total of 105 subsequent pregnancies, resulting in 82 (78.1%) live births, 18 (17.1%) spontaneous abortions, and 5 (4.8%) terminations. Twenty-three of the 48 women (56.1%) diagnosed with PPCM had a total of 37 subsequent pregnancies resulting in 25 (67.6%) live births, 5 (13.5%)

spontaneous abortions, and 7 (18.9%) terminations (Table 5.6). Pregnancy termination was significantly higher in cases compared with controls (P = .01) (Table 5.6). Among the women diagnosed with PPCM, 10 (30.3%) of the subsequent pregnancies were planned, 23 (65.2%) were unplanned, with information unavailable regarding planning for 6 pregnancies (Table 5.6). Twenty-two of the women (95.7%) recovered cardiac function (LVEF of 50% per follow-up echocardiography) before subsequent pregnancy. One woman had no follow-up echocardiograms after index pregnancy diagnosis, so recovery status at subsequent pregnancy was unknown (Fig. 5.1). Fifteen women (65.2%) were on cardiac medication during their subsequent pregnancies (Table 5.6). The relapse rate in the PPCM cohort was 12.5% (n = 6), but all 6 cases recovered normal LV function after their relapse (Table 5.6 and Fig. 5.1). Similar rates of women in each cohort underwent sterilization procedures after index delivery (33.3% vs 34.4%, P = .90).

Discussion

The estimate of the incidence of PPCM in Olmstead County, Minnesota from 1970 through 2014 was 20.3 cases per 100,000 live births, which is lower than previous estimates of 25 to 185 per 100,000 live births.[5-7,9,13,23] Fifteen cases were found in Olmsted County and an additional 33 cases for a total of 48 cases in the larger 27 county region. However, owing to the lower percentage coverage rate (61%) for the REP in the 27 county region, PPCM incidence for the larger region could not be calculated. From an initial 1177 patients identified using diagnosis codes for heart failure, cardiomyopathy and PPCM, only 48 (55%) of the 88 women with a diagnosis code for PPCM met the diagnostic criteria for PPCM after record review by a physician experienced with PPCM (Fig. 5.1).[1] The most common reasons for exclusion included a LVEF of >45% and a diagnosis of other types of

cardiomyopathy (Fig. 5.1). Our study may reflect a more accurate population-level incidence than previously published studies, because all cases in this study were confirmed using medical record data, whereas previously published studies[5-7,9,13,23] relied on diagnosis codes and may have overestimated the disease incidence by including women who had the diagnosis code for PPCM in their medical record but did not meet the diagnostic criteria for PPCM.

The mean age at PPCM diagnosis in this study was28 years (Table 5.1), with 62.5% of cases occurring in women 30 years in contrast with previous studies that found an association between PPCM diagnosis and advanced maternal age.[6,8,9,13] Previous studies reported that Black women have the highest rates of PPCM, followed by non-Hispanic White women, with Hispanics and Asians having the lowest rates.[5,6,9,13,23-25] Based on US Census data, the population within the study area was 90.2 97.4% non-Hispanic White and 1.3 3.7% Black during the study period, whereas cases in this cohort were 79.2% non-Hispanic White and 18.8% Black, supporting previous reports that PPCM cases seem to occur at a higher rate among Black women compared with non-Hispanic White women.[15]

Previous reports have also suggested an increased risk of PPCM with multiparty[5,8-12] and multifetal gestation.[26] In the current study, we did not observe an association between multiparity and PPCM diagnosis, as 28 of the 48 women (58.3%) with PPCM were nulliparous (Table 5.3). Similar to previous studies, however, multifetal gestation during the index pregnancy (17.0%, n = 8 in cases) occurred at a higher rate in women diagnosed with PPCM compared with the national rates for multifetal gestation that ranged from 2.1% to 3.5% during the time period of this study.[27]

HDP have been associated with an increased risk of PPCM.[26,28,29] Twenty-seven of the cases (56.3%) in this study were diagnosed with HDP during their index pregnancy, a rate significantly higher than controls (12/96, 12.5%, *P* .001) (Table 5.4). Preeclampsia was the most common HDP diagnosis among cases, occurring in 18 of the 48 women (37.5%) (data not shown), which is more than nine times the 4% preeclampsia rate among women in the United States.[30] This finding aligns with previous studies that have reported that preeclampsia is one of the strongest risk factors for PPCM.[26,31]

This study identified prior diagnoses of anxiety or migraine as novel possible risk factors for PPCM (Table 5.2). Anxiety may increase the risk of cardiovascular disease by increasing inflammation and inducing endothelial dysfunction, 2 factors that are postulated to play a role in the pathogenesis of PPCM.[32] Migraine may also be a risk factor for developing PPCM, although with a small sample size of incident cases, this may also simply reflect migraine as a common disease state in women. It is important to note, however, that migraine is a known risk factor for cardiovascular and cerebrovascular disease, potentially increasing risk through pathways including HDP.[33-35] Migraine, pre-eclampsia, and PPCM have all been associated with vascular dysfunction owing to hormone imbalances and angiogenic factors including vascular endothelial growth factor, soluble fms-like tyrosine kinase-1, estrogen, relaxin-2, prolactin, and placental growth factor.[33,36-41] Further investigation, including determining whether or not migraine subtype (with or without aura, for example) is more predictive of PPCM and whether increased frequency of migraine during pregnancy or only postpartum heightens risk of PPCM, is warranted.

Similar to previous studies,[5,8,42,43] the findings from this study suggest that infants born to mothers with PPCM have an increased risk for adverse birth outcomes, including pre- maturity and low birthweight (<2500 g) compared with those born to mothers in the control cohort (Table 5.4). These adverse outcomes are important to note, because premature birth and low birth weight are both associated with increased infant mortality and a variety of developmental and medical issues for the child.[44]

Another important finding in this study is that the rate of breastfeeding in women with PPCM decreased significantly after diagnosis (Table 5.4). Women discontinued breastfeeding for a variety of reasons, including their perceived compromised physical or mental health, not having ready access to their infants while hospitalized, a lack of awareness by treating physicians about the safety of cardiac medications during lactation, and/or a concern that breastfeeding may be detrimental to the mother's recovery based on the proposed mechanistic link between PPCM and the nursing hormone prolactin.[37,45] The World Health Organization recommends exclusive breast- feeding for 6 months and continued breastfeeding for 1 2 years[46] because the lack of breastfeeding is associated with an increased risk of diabetes, ovarian and breast cancers, and postpartum depression in women and higher rates of mortality, infections, eczema, asthma, childhood obesity, diabetes, leukemia, and lower intelligence in children.[47,48] Mothers with PPCM and their physicians would likely benefit from increased education and awareness regarding which cardiac medications are safe to use during lactation and that breast- feeding seems to have no detrimental effect on outcomes among women with PPCM according to several published reports.[49-51] Further investigation into the short- and long- term outcomes of

infants born to mothers diagnosed with PPCM is necessary so that appropriate counseling and care can be provided to mothers and infants.

Nearly 90% of the women with PPCM in this study recovered normal LV function with a median recovery time of 4.5 months (Table 5.5). It should be noted that approximately one- half of the women who had not recovered by year one did not have follow-up echocardiograms until 1 12 years after diagnosis, at which time they had recovered. Owing to the retrospective nature of the study, the precise timing of recovery was difficult to establish. However, our data suggest that cardiac function can continue to improve for many years after PPCM diagnosis. Guideline-directed recommendations for follow-up assessment of women diagnosed with PPCM would likely enhance our understanding regarding degree and timing of LV recovery in patients.

In our study, 5 of 43 woman (11.6%) with PPCM who recovered LV function suffered a decline in cardiac function, between 6 months to 9.3 years after recovery, unrelated to a subsequent pregnancy (data not shown). One woman suffered cardiac toxicity from medications taken for an unrelated condition and recovered. A second woman recovered by one year and then had 2 occasions with deterioration in cardiac function despite remaining on cardiac medications throughout that time period with her most recent echocardiogram demonstrating a LVEF of 50%. Three women had discontinued all cardiac medications after recovery but then suffered declines in cardiac function at 3.5, 6.0, and 9.3 years after recovery. All 3 women recovered cardiac function after cardiac medications were restarted. Most medical experts agree that guideline- directed medical therapy for heart failure should be continued indefinitely in women with PPCM who have persistent cardiac dysfunction. However, there is no clear consensus on how to treat women with

PPCM with recovered LV function.[2,52]Data regarding the long-term risk of cardiac deterioration if medications are stopped is conflicting.[53,54] Two recent studies suggest that women with LV recovery may still have LV diastolic dysfunction, decreased exercise capacity, ongoing angiogenic imbalance, and residual myocardial injury.[55,56] Noting that 5 women in our PPCM cohort experienced decline in LV function after recovery unrelated to subsequent pregnancy high- lights the difficulty in determining the duration of medical treatment after recovery and the importance of long-term regular cardiac follow-up for women diagnosed with PPCM, including those with recovered cardiac function.

Many women with PPCM desire to have additional pregnancies after diagnosis. Decisions regarding subsequent pregnancy are challenging, because all women with PPCM are at risk for a decrease in LV function and possibly even death. Experts agree that women with persistent significant cardiac dysfunction are at greatest risk for cardiac complications during subsequent pregnancy and should be counseled against future pregnancy, while women with recovered cardiac function may consider subsequent pregnancy.[2,57,58] There are no proven risk factors for relapse during subsequent pregnancy among women with recovered LVEF, so careful monitoring during and after pregnancy is indicated. Although the sample size is small, our study results support the consensus that women diagnosed with PPCM with recovered cardiac function can have successful subsequent pregnancies (Table 5.6). Of note, 4 of the women in our study who relapsed during subsequent pregnancy were on cardiac medications at the time of relapse, highlighting that heart failure therapy does not guaran- tee freedom from relapse (Table 5.6). In addition, the large number of unplanned subsequent pregnancies and the higher rate of terminations in women

diagnosed with PPCM indicate that contraceptive counseling on an ongoing basis, not simply shortly after PPCM diagnosis, is critical.

There are several limitations to this study. The small sample size prevented any subgroup analysis. The lack of racial/ethnic diversity in the REP compared with other regions of the United States may limit the generalizability of the study. Owing to the retrospective nature of the study, data are restricted to what is available in medical records and therefore the timing of subsequent echocardiograms varied between patients, adding uncertainty to calculations such as length of time to recovery. In addition, some cases of PPCM may have been missed because the REP does not have complete coverage of medical records for all 27 counties. This factor prevented an incidence calculation for the entire study area. A major strength of our study, however, is the use of data from the REP, a well-established, high-quality, federally funded resource for epidemiologic research. In addition, the use of complete medical record review to confirm the diagnosis leading to a well-defined cohort of PPCM cases from a specific geographical area with long- term follow-up is particularly noteworthy. These strengths, as well as the almost complete capture rate of medical records for all residents of Olmsted County, Minnesota, made it possible to calculate a precise incidence estimate for that area.[14-16] These strengths, along with the verification of diagnosis by medical record review, minimized referral bias and misclassification, which are common in coding-based studies. This study was also strengthened by the range of data collected and analyzed, as well as the abundance of data in areas addressing knowledge gaps related to PPCM including long-term outcomes of mothers, infant outcomes, and outcomes of subsequent pregnancies.

Conclusions

The population-based incidence of PPCM was 20.3 cases per 100,000 live births in Olmsted County, Minnesota. Among the well-characterized cohort of women with PPCM in this study, a history of anxiety and a history of migraine emerged as novel risk factors. The majority of women recovered LV function days to years after diagnosis. A minority of women with recovered LV function experienced subsequent LVEF decline months to years after recovery. Infants of mothers with PPCM had an increased risk of prematurity and low birth weight. Finally, women with recovered LVEF before subsequent pregnancy experienced no long-term decline in LVEF after pregnancy.

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Table 5.1 Maternal demographic characteristics of cases and controls*

Patient Characteristics	**Case** (*n*=48)	**Control** (*n*=96)	***p* value**
Age (y)	28 ± 7.0	28 ± 7.0	-
Pre-pregnancy BMI (kg/m$^{2)}$	25.2 (20.5-36.6)	23.6 (21.6-28.03)	.01
BMI Category			.005
<25.0	16 (33.3)	56 (58.3)	
≥25.0	32 (66.7)	40 (41.7)	
Race/Ethnicity			-
White	38 (79.2)	76 (79.2)	
American Indian	1 (2.1)	2 (2.1)	
Black	9 (18.7)	18 (18.7)	
African American	3 (6.2)	7 (6.2)	
African Immigrant	6 (12.5)	11 (12.5)	
Hispanic	1 (2.1)	2 (2.1)	
Marital Status			.07
Single	13 (27.1)	26 (27.1)	
Married	24 (50.0)	61 (63.5)	
Domestic Partner	11 (22.9)	9 (6.4)	
Education			
< High school	6 (13.3)	13 (13.7)	.84
High school or GED	12 (26.7)	19 (20.0)	
Some college or associate degree	15 (33.3)	36 (37.9)	
≥ College degree	12 (26.7)	27 (28.4)	
Health Insurance			.001
Private	21 (46.7)	70 (74.4)	
Medical assistance / Medicaid	24 (53.3)	24 (25.6)	
Smoking			.16
At diagnosis	15 (31.2)	16 (18.0)	
Before pregnancy	8 (16.7)	23 (25.8)	
Never	25 (52.1)	50 (56.2)	
Alcohol Use			.44
At diagnosis	3 (6.5)	1 (1.6)	
Before pregnancy	24 (52.2)	37 (57.8)	
Never	19 (41.3)	26 (40.6)	
Drug Use			.82
Current	3 (6.2)	3 (3.8)	
Past	7 (14.6)	11 (14.1)	
Never	38 (79.2)	64 (82.1)	
Length of follow-up† (y)	7.2 (4.1 – 12.6)	12.8 (8.2 – 18.8)	<.001

Data are *n* (%), mean ± standard deviation, or median (interquartile range) unless otherwise specified.

*Percentages are based on column totals excluding unknown data.

†Follow-up was defined as years of medical records available for review post index pregnancy. Abbreviations: BMI, body mass index; GED, general educational development or general education diploma.

Table 5.2 Medical history of cases and controls

Comorbidity	**Case** (*n*=48)	**Control** (*n*=96)	***p* value**
Hypertension	4 (8.3)	2 (2.1)	.01
Hyperlipidemia	1 (2.1)	6 (6.3)	.43
All Heart Disease[*,†]	3 (6.3)	7 (7.3)	.99
Arrhythmia	3 (6.3)	3 (3.1)	.39
Other Heart Disease[†]	0 (0.0)	4 (4.2)	.55
Cancer[‡,§]	2 (4.2)	2 (2.1)	.60
Any Mental Health Diagnosis	26 (54.2)	35 (36.5)	.04
Depression	22 (45.8)	31 (32.3)	.14
Anxiety	12 (25.0)	10 (10.4)	.03
Other Mental Health Diagnosis	15 (31.3)	18 (18.8)	.10
Asthma	11 (22.9)	18 (18.8)	.66
Allergies[§]	23 (47.9)	33 (34.4)	.15
Infections	28 (58.3)	55 (57.3)	.91
Diabetes	0 (0.0)	2 (2.1)	.55
Migraines	21 (43.8)	15 (15.6)	<.001
Autoimmune Disease[‖]	0 (0.0)	5 (5.2)	.17
Chemical Exposure[¶]	6 (12.5)	4 (4.2)	.08

Data are *n* (%) or mean (range) unless otherwise specified.
Percentages are based on column totals excluding unknown data.
[*]Three cases with arrhythmia.
[†]The controls with mitral valve prolapse, three controls with arrhythmia, one control with patent foramen ovale.
[‡]Two cases had malignant melanoma, both treated only with excision.
[§]One control had thyroid cancer treated with excision and iodine ablation and one control had laryngeal squamous cell carcinoma treated with excision.
[‖]One control with ulcerative colitis, one control with Graves' disease and three controls with Hashimoto's thyroiditis.
[¶]Two cases with black mold exposure, two cases with pesticide exposure, two cases with occupational exposure.

Table 5.3 Obstetric history of cases and controls prior to index pregnancy*

Obstetric history	**Case** (*n*=48)	**Control** (*n*=96)	***p* value**
Parity			
Median Parity†	1 (0-2.5)	1 (0-2.5)	.34
Nulliparous	28 (58.3)	43 (44.8)	.16
Primipara or multipara	20 (41.7)	53 (55.2)	.16
Primipara or multipara women	*n*=20	*n*=53	
Multi-fetal gestations	0 (0.0)	0 (0.0)	-
Hypertensive disease of pregnancy‡	8 (40.0)	4 (4.2)	.02
Gestational diabetes§	1 (4.8)	3 (3.1)	.04

Data are *n* (%) or mean (range) unless otherwise specified.
Percentages are based on column totals excluding unknown data.
*The index pregnancy is the pregnancy associated with initial peripartum cardiomyopathy diagnosis for cases and the matched pregnancy for controls.
†Parity ranged from 0 to 6 for cases and 0 to 5 for controls.
‡Hypertensive disorders of pregnancy includes gestational hypertension, preeclampsia, eclampsia, preeclampsia superimposed on chronic hypertension, and unspecified types. Six missing.
§Five missing.

Table 5.4 Index pregnancy characteristics of cases and controls*

Characteristic	Case (*n*=48)	Control (*n*=96)	*p* value
Assisted reproduction	4 (8.3)	13 (13.5)	.42
Access to standard medical care during pregnancy	27 (75.0)	78 (82.1)	.36
Planned Pregnancy	11 (32.4)	50 (54.4)	.03
Single Parenting	10 (20.8)	21 (23.1)	.96
Hypertensive disease of pregnancy	27 (56.3)	12 (12.5)	<.001
Gestational diabetes	2 (4.4)	9 (9.5)	.50
Antibiotic use during pregnancy	21 (70.0)	53 (56.4)	.19
Bed rest	11 (28.2)	12 (12.6)	.03
Tocolytic therapy	2 (4.3)	11 (11.6)	.22
Method of delivery			.001
Spontaneous vaginal	16 (33.3)	59 (61.5)	.001
Assisted vaginal	6 (12.5)	12 (12.5)	.99
Planned caesarian section	5 (10.4)	11 (11.5)	.85
Emergency caesarian section	21 (43.8)	14 (11.6)	<.001
Indication for caesarean section			
Cardiac	11 (55.4)	1 (7.1)	.01
Obstetric	10 (47.6)	13 (92.9)	
Number of neonates			
Single	40 (83.3)	80 (83.3)	-
Twins	7 (14.9)	14 (14.9)	
Triplets	1 (2.1)	2 (2.1)	
Neonate sex			.68
Male	23 (41.8)	51 (45.1)	
Female	32 (58.2)	62 (54.9)	
Gestational age (wks)	36 (23-39)	37 (37-40)	.004
Premature (< 37 weeks)	21 (43.8)	22 (22.9)	.003
Birthweight (*g*)	2,445 (2012-3459)	3,190 (2550-3562)	.01
Low birth weight (<2,500 *g*)	22 (45.8)	28 (24.8)	.01
Breastfeeding			
Yes	22 (59.5)	69 (75.8)	.06
Breastfeeding in cases only			
After delivery	22 (59.5)	-	.009
Post diagnosis	9 (24.3)	-	

Data are n (%) or median (interquartile range) unless otherwise specified.
Percentages are based on column totals excluding unknown data.
*The index pregnancy is the pregnancy associated with initial peripartum cardiomyopathy diagnosis for cases and the matched pregnancy for controls.

Table 5.5 Disease characteristics of women diagnosed with PPCM (*n*=48)

Disease Characteristic	Value
Timing of Diagnosis[*] (days)	4 (0 - 12)
During pregnancy	11
Postpartum	37
Clinical Features	
Blood pressure	
Systolic (mmHg)	140 (126 - 154)
Diastolic (mmHg)	89 (79 - 104)
Elevated[†]	41 (85.4)
Heart rate (bpm)	103.5 (88 - 120)
Murmur [‡]	14 (29)
Signs suggestive of left heart failure[§]	
Yes	36 (75.0)
Unknown	2 (4.2)
Signs suggestive of right heart failure[¶]	
Yes	33 (68.8)
Unknown	5 (10.4)
Echocardiograph Parameters	
EF (%)	34 (24 – 40)
LVEDD (cm)	5.7 (5.1 – 6.0)
LVESD (cm)	4.5 (4.1 – 4.0)
Ventricular septal wall thickness (cm)	1.0 (0.9 – 1.1)
Posterior wall thickness (cm)	0.9 (0.9 – 1.1)
RV enlargement[‡]	9 (18.8)
RV hypokinesis[‖]	16 (33.3)
LA volume index (mL/m^2)	34 (27 – 38)
Valvular heart disease[#,‖]	20 (41.7)
Pericardial effusion[‖]	20 (41.7)
Treatments	
Treatment with medication	47 (97.9)
ACE inhibitor	42 (87.5)
Angiotensin II receptor blocker	2 (4.2)
Beta blocker	38 (79.2)
Diuretic	42 (87.5)
Blood thinner	17 (35.4)
Bromocriptine	0 (0.0)
Vasodilator	10 (20.8)
Anti-arrhythmic	10 (20.8)
Calcium channel blocker	2 (4.2)
Nitroglycerin	3 (6.3)

Potassium	4 (8.3)
Magnesium sulfate	4 (8.3)
Mechanical circulatory support	0 (0.0)
Cardiac device implantation[**]	1 (2.1)
VAD	0 (0.0)
Outcomes	
Length of follow-up after diagnosis (y)	7.3 (4.1 – 12.2)
Transplant	0 (0.0)
Death	1 (2.1)
Left ventricular recover[††,‡‡]	43 (89.6)
Persistent cardiac dysfunction[§§]	2 (4.2)

Data are n (%) or median (interquartile range) unless otherwise specified.
Percentages are based on column totals excluding unknown data.
[*]Diagnosis timing ranged from 2 days before delivery to 185 days (6 months) postpartum with 7 women diagnosed on the day of delivery.
[†]Elevated blood pressure as defined as a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg as in the 2020 International Society of Hypertension Global Hypertension Practice Guidelines.[22]
[‡]Seven missing.
[§]Rales, wheezing, pulmonary edema.
[¶]Jugular venous distension, ascites, peripheral edema.
[‖]Eight missing.
[#]Designation of valvular heart disease was based on echocardiogram interpretations and included disease categorized as mild/moderate, moderate, moderate/severe, or severe. Valvular disease was found in just the mitral valve in 11 patients and in just the tricuspid valve in 6 patients. An additional 2 patients had disease in both the mitral and tricuspid valves and 1 patient had disease in the mitral, tricuspid, and pulmonary valve.
[**]Intra-aortic balloon pump.
[††]Left ventricular recovery defined as a left ventricular ejection fraction of ≥50% by echocardiogram.
[‡‡]Recovery time ranged from 3 days to just >12 years with a median of 4.5 months. Two patients had residual dysfunction, 1 died, and 2 had no follow-up echocardiogram, so the official recovery status is not known, but both were functionally recovered.
[§§]Persistent cardiac dysfunction defined as a left ventricular ejection fraction of ≤50%.
Abbreviations: ACE, angiotensin-converting enzyme; bpm, beats per minute; EF, ejection fraction; LA, left atrial; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; RV, right ventricle; VAD, ventricular assist device.

Table 5.6 Obstetric and cardiac outcomes of subsequent pregnancy of cases and controls

Outcomes	**Case** (*n*=48)	**Control** (*n*=96)	***p* value**
Number of women w/ subsequent pregnancies	23 (56.1)	56 (62.6)	.46
Subsequent pregnancies[†]	(*n*=37)	(*n*=105)	
Planned	10 (30.3)	‡	-
Unplanned	23 (69.7)	‡	-
Pregnancy outcome			
Delivered	25 (67.6)	82 (78.1)	.20
Spontaneous abortion	5 (13.5)	18 (17.1)	.80
Terminated	7 (18.9)	5 (4.8)	.01
Women on cardiac medication	15 (65.2)	‡	
Beta Blocker[§]	14	‡	
Calcium channel blocker	1	‡	
Digoxin	1	‡	
Maternal Outcome			
Relapse[¶]	6 (12.5)	‡	-
On cardiac medication at time of relapse	4 (66.7)	‡	
Recovery after relapse[‖]	6 (100.0)	‡	-
Sterilization	16 (33.3)	33 (34.4)	.90

Data are number (%) unless otherwise specified.
Percentages are based on column totals excluding unknown data.
[*]For 7 cases and 7 controls subsequent pregnancy status is unknown.
[†]For 4, subsequent status, no data are available regarding planning of pregnancy.
[‡]Data either not applicable or not obtained.
[§]One woman was treated with both a beta blocker and a calcium channel blocker.
¶Relapse defined as decrease in the left ventricular ejection fraction to ≤45%.
[‖]LV recovery defined as a left ventricular ejection fraction of ≥50% by echocardiogram.

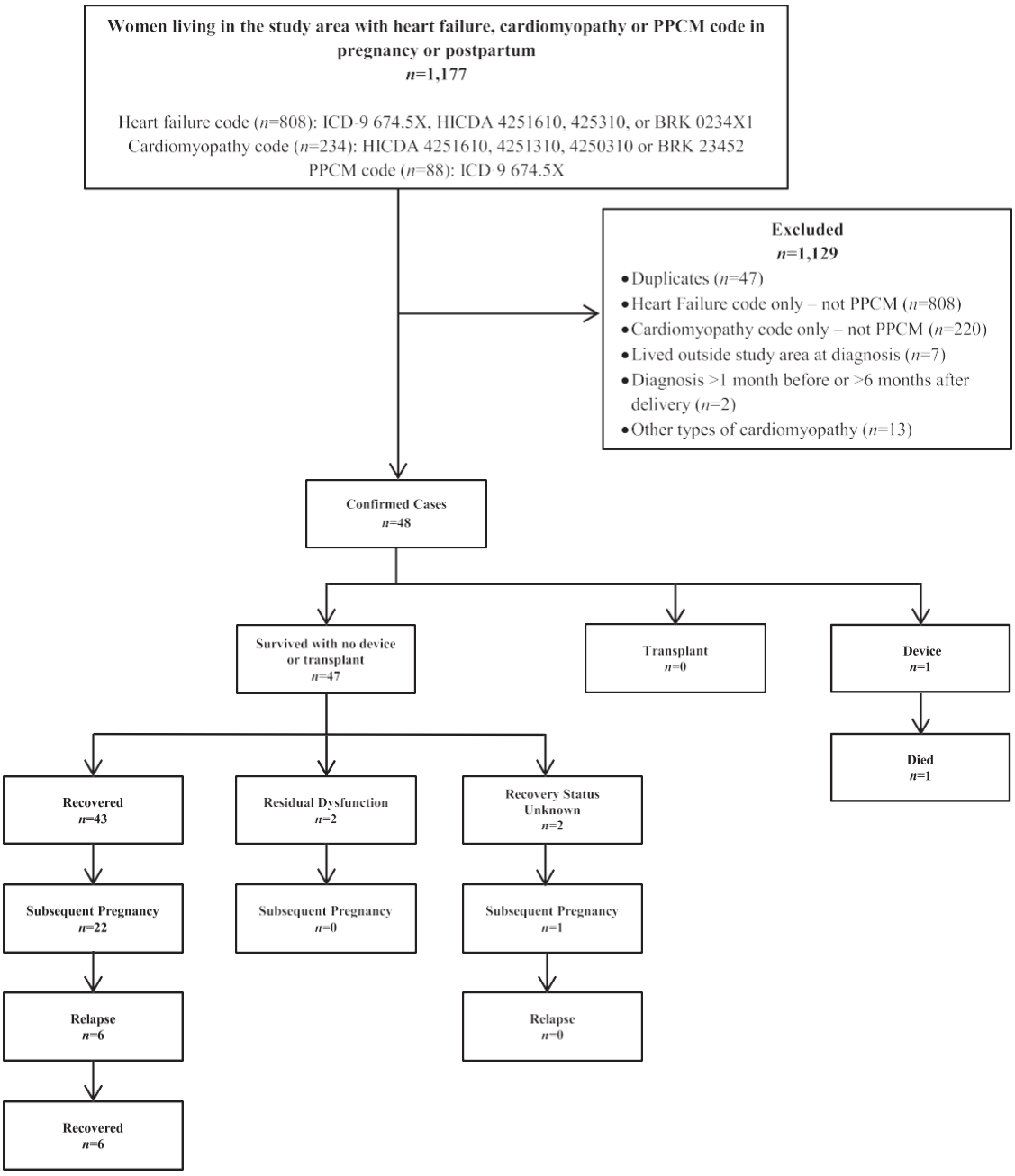
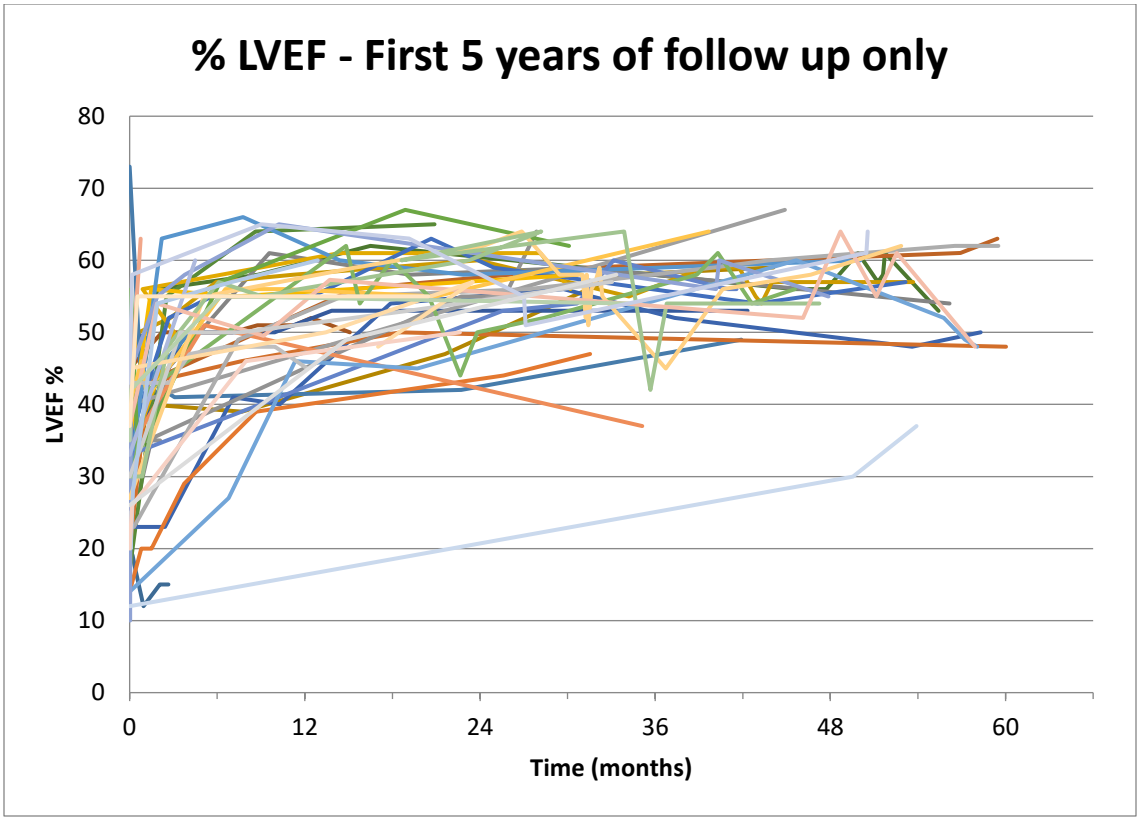


Figure 5.1 Patient cohort with outcomes.

From an initial cohort of 1177 women, 48 cases of peripartum cardiomyopathy (PPCM) were con- firmed. 47 out of 48 women survived. One woman received an intra-aortic balloon pump and subsequently died. There were no transplants in this cohort. 43 women recovered cardiac function (left ventricular ejection fraction of 50% on echocardiogram), 2 had residual left ventricular dysfunction, and 2 had no follow-up echocardiograms so the recovery status could not be determined, but both were functionally recovered. At least 22 of the recovered women had subsequent pregnancies, as well as 1 woman whose recovery status was unknown. One woman with unknown recovery status (functionally recovered)

had 1 subsequent pregnancy and did not relapse symptomatically, but no echocardiogram was conducted. Six of the recovered cases relapsed (12.5% rate of relapse) with at least 1 pregnancy, but all 6 subsequentlyrecovered after relapse.



Supplemental Figure 5.1 Trends in LVEF for confirmed cases of PPCM.

Data for the first 5 years post diagnosis are included in the graph, although follow-up echocardiograms are available for some patients up to 25.6 years after diagnosis. The time to recovery ranged from 3 days to just over 12 years based on echocardiography with an average time to recovery of just under one year. One patient died without recovery, two patients had residual dysfunction, and two patients did not have follow-up echocardiograms but were considered to be functionally recovered.

Chapter 6: The Potential Relationship between Air Pollution Exposure and Peripartum Cardiomyopathy

In 2014, air pollution was identified as the largest single environmental health risk factor for death worldwide and was related to multiple adverse health outcomes including cancer, respiratory diseases, and CVDs.[1,2] One type of air pollution, particulate matter (PM) was found to be responsible for 3.2 million deaths in 2010 and was reported to be the 9th leading cause of disability adjusted life-years worldwide.[3,4] PM can be of various sizes and arises from a variety of sources. PM is generally classified by size into 3 categories using the mean aerodynamic diameter of the particles. The largest particles are termed "coarse PM" or PM_{10} and consist of particles between 2.5μm and 10μm. Smaller particles that are <2.5μm are called "fine PM" or $PM_{2.5}$. And finally, "ultrafine particles" are <0.1μm in size. PM_{10} particles are mainly composed of soil and road dust suspended by wind or moving vehicles, construction activity like grinding and digging, and road wear of brake pads on vehicles. $PM_{2.5}$ is predominantly a byproduct of combustion of fossil fuels created by vehicles and power plants, or through the burning of coal, oil, and wood for industrial and residential heating. Outdoor pollution (especially $PM_{2.5}$) is found inside buildings and therefore exposure to outdoor pollution may occur indoors. In low-income countries, indoor air pollution is greater than in high-income nations due to the common use of fossil fuels (i.e., coal, wood, biomass) for cooking and heating homes, schools, and the work place.[1,2,5,6]

In an effort to reduce adverse health effects related to ambient air pollution, many countries as well as the World Health Organization (WHO) have released exposure guidelines for each major air pollutant including PM. The US Environmental Protection Agency (EPA) sets the annual mean exposure limit in the US for $PM_{2.5}$ at 12μg/m^3 while the WHO sets the limit at 10μg/m^3.[1,7] While EPA and WHO guidelines have helped to reduce ambient air pollution, the reality is that levels of $PM_{2.5}$ regularly exceed these guidelines in most large cities in the US and in many places throughout the world.[2,6,8] Importantly, even the lowest levels of $PM_{2.5}$ have been found to cause adverse health effects, suggesting that there is no safe minimum exposure level for $PM_{2.5}$.[1,2,6,9]

Epidemiological studies have established a causal relationship between ambient $PM_{2.5}$ exposure and CVD.[4-6,9] Both short and long-term exposure to $PM_{2.5}$ increases the risk of ischemic heart disease, MI, stroke, arrhythmia, and heart failure and increases the risk of hospitalization and mortality due to CVD.[6] Although the underlying pathophysiological mechanisms are still being investigated, $PM_{2.5}$ is believed to promote CVDs, including cardiomyopathy, through two main mechanisms.[5,6,9,10] The first mechanism is that air pollution activates the pulmonary autonomic nervous system leading to increased blood pressure which promotes endothelial dysfunction and hypertension, resulting in poor cardiac output and heart failure. (Figure 6.1) Secondly, $PM_{2.5}$ also activates ROS, causing an inflammatory response in the lungs that leads to endothelial dysfunction, elevated blood pressure, hypertension and heart failure (Fig. 6.1). The most recent Integrated Science Assessment for Particulate Matter (ISA for PM) the U.S. Environmental Protection Agency[11] also suggest similar mechanisms in their chapter on cardiovascular disease. (Figure 6.2)

The clear overlap in proposed mechanisms for CV dysfunction caused by air pollution and those proposed for prolactin suggest that PM may act as a trigger to increase the risk of PPCM in susceptible individuals. We hypothesize that PM could act a co-factor in triggering PPCM by contributing to oxidative stress (as a source of ROS) and endothelial dysfunction that may lead to cardiomyopathy (see Figure 6.3).[12] To our knowledge, no one has examined whether PM is a risk factor for PPCM. Chapter Seven presents a case study using the cohorts described in Chapter Four to examine the ability of three commonly available methodologies (air monitoring, traffic density, and distance to major roadways) to ascertain the role of $PM_{2.5}$ exposure in the development of PPCM, the challenges that prevented each method from being fully applied, policy-based recommendations that would allow studies to successfully determine whether $PM_{2.5}$ exposure leads to increased susceptibility to developing PPCM and recommendations that could strengthen the human health protection required by the Clean Air Act (CAA). The specific components of Aim 2 needed to be modified for Aim 2 because of challenges that arose in being able to determine PM exposure for the study. These challenges are presented as a case study in Chapter Seven. Because of the challenges the sub aims for Aim 2 of this research project were modified to: a) Identifying and comparing different methodologies for measuring air pollution exposure in rural areas, and b) creating a case study of these methodologies using the PPCM case-control cohort developed in Aim 1.

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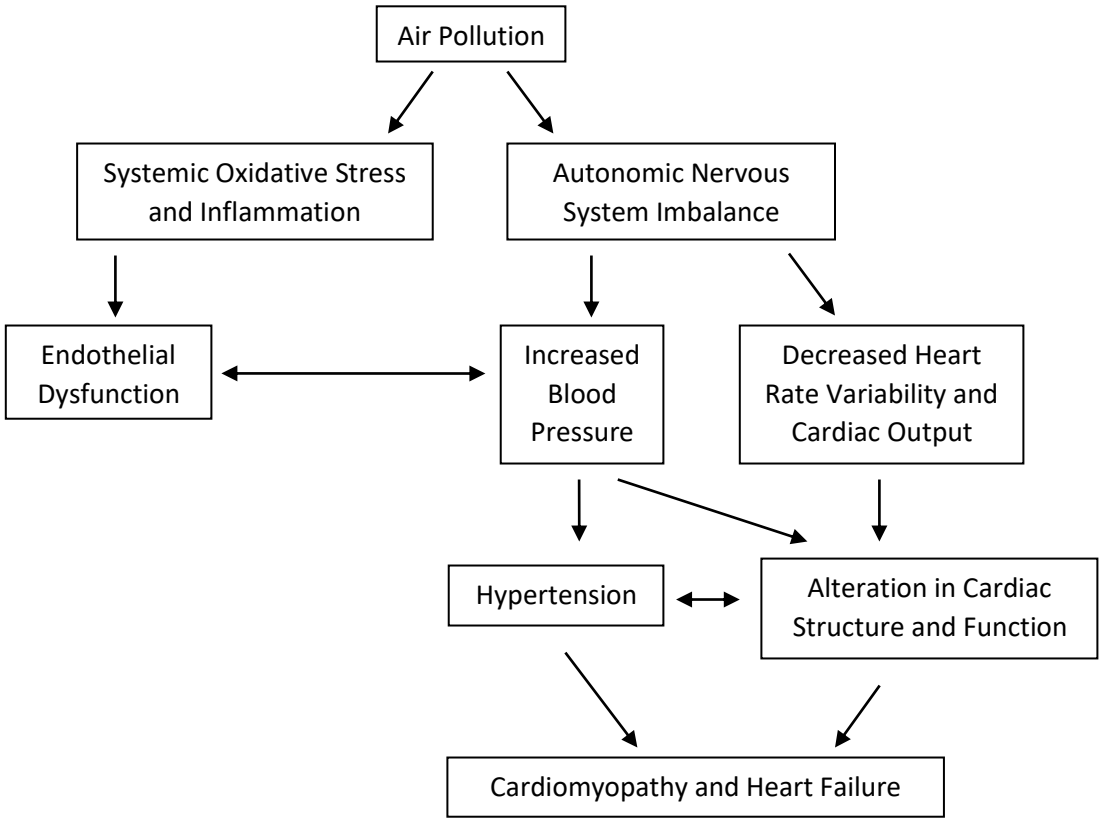

Figure 6.1 Potential biological pathway for the role of air pollution exposure (including $PM_{2.5}$) in the development of heart failure, cardiomyopathy, and peripartum cardiomyopathy.

Exposure to air pollution can lead to systemic oxidative stress (i.e., reactive oxygen species) as well as an imbalance in the autonomic nervous system. These physiological changes affect multiple factors including endothelial function, blood pressure, cardiac output, and heart rate, which may result in cardiomyopathy or heart failure. Figure adapted from[11] Cosselman, K. E., Navas-Acien, A., & Kaufman, J. D. (2015). Environmental factors in cardiovascular disease. Nat Rev Cardiol, 12(11), 627-642. doi: 10.1038/nrcardio.2015.152.[9]

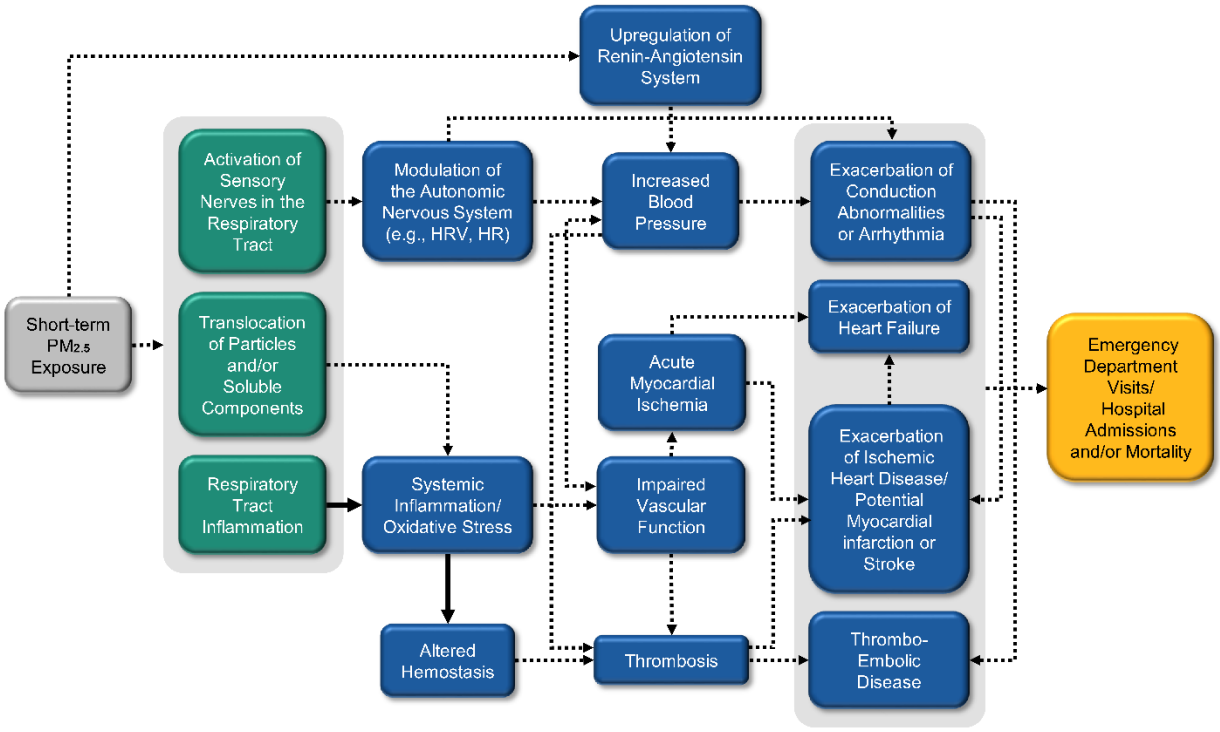

Figure 6.2 Biological pathways for cardiovascular effects following short-term exposure to PM2.5.

HR = heart rate; HRV = heart rate variability; PM2.5 = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm.

Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence related to short-term PM2.5 exposure, and the arrows indicate a proposed relationship between those effects. Solid arrows denote evidence of essentiality as provided, for example, by an inhibitor of the pathway or a genetic knockout model used in an experimental study involving PM2.5 exposure. Shading around multiple boxes is used to denote a grouping of these effects. Arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes. Progression of effects is generally depicted from left to right and color coded (gray = exposure; green = initial effect; blue = intermediate effect; orange = effect at the population level or a key clinical effect). Here, population-level effects generally reflect results of epidemiologic studies. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure and text copied from 6-1 From the U.S. EPA Integrated Science Assessment for Particulate Matter[11]

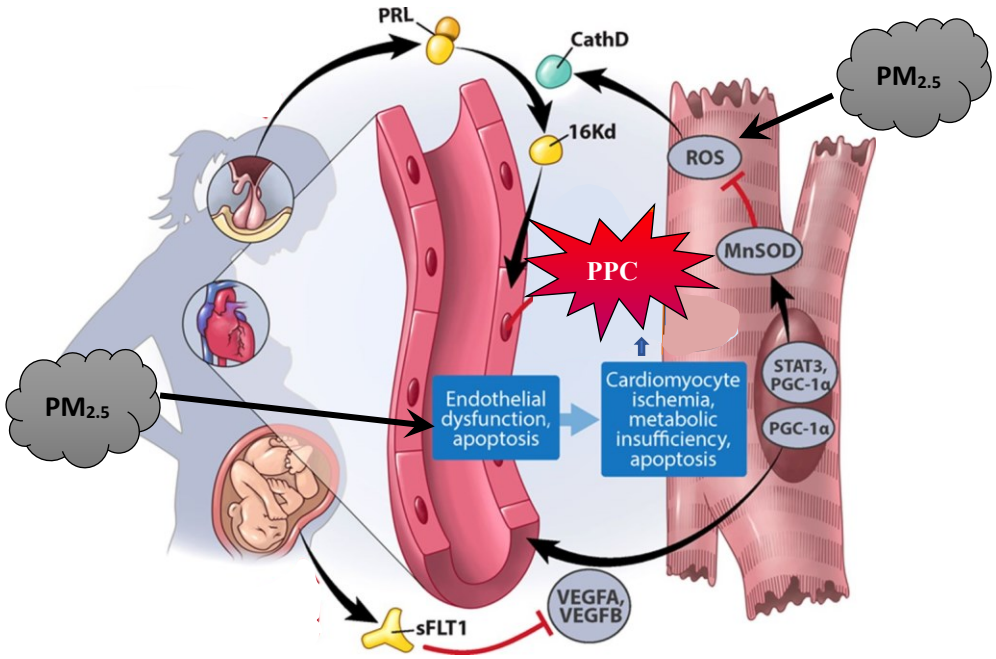

Figure 6.3 Proposed mechanism for the role of $PM_{2.5}$ in PPCM.

$PM_{2.5}$ could increase susceptibility to PPCM by increasing oxidative stress leading to increased reactive oxygen species and / or by causing endothelial dysfunction, which are part of the currently accepted mechanism for the development of PPCM. Abbreviations: STAT3, signal transducer and activator of transcription 3; PGC-1α, proliferator-activated receptor-gammacoactivator-1α; sFlt1, soluble Fms-like tyrosine kinase 1; 16Kd, 16-kDa form of prolactin; MnSOD, manganese superoxidedimutase; CathD, cathepsin D; PRL, prolactin; VEGF-A/B, vascular endothelial growth factors; ROS, reactive oxygen species. Figure adapted from Arany, Z., & Elkayam, U. (2016). Peripartum Cardiomyopathy. Circulation, 133(14), 1397-1409. doi: 10.1161/circulationaha.115.020491.[12]

Chapter 7: A Case Study on Strengthening the Clean Air Act: Peripartum Cardiomyopathy and the Rochester Epidemiology Project*

***Note**: The formatting of this manuscript differs from the other three manuscripts presented in this dissertation because it has been formatted for submission to *The Environmental Law Reporter* (ELR). The ELR is a legal publication that addresses the legal and/or policy aspects of environmental issues and as such has a different formatting style then medical and scientific journals.

Introduction/ Background

The Clean Air Act (CAA)[i] is one of the fundamental laws of the United States protecting public health, welfare, and the environment by setting air quality standards and regulating air pollutant emissions from both stationary and mobile sources. One of the central components of the CAA is the requirement that the U.S. Environmental Protection Agency (EPA) must develop health based primary and secondary national ambient air quality standards (NAAQS) for "criteria pollutants" that include 6 common air pollutants or pollutant groups: sulfur dioxide, particulate matter ($PM_{2.5}$ and PM_{10}), nitrogen dioxide,

[i] 42 U.S.C. §§7401-7671q, ELR Citation: ELR STAT. CAA §§101-618

carbon monoxide, ozone, and lead. The NAAQS must be set at levels that protect public health with an adequate margin of safety and to protect public welfare from any known or anticipated adverse effect.[1] The CAA requires that the EPA review the scientific data for each of these criteria pollutants and revise the NAAQS in relation to any new data as necessary every 5 years. The responsibility for attaining and maintaining these standards is placed with the states, and each state must provide plans and updates on progress to the EPA.

For particulate matter (PM) the EPA regulates and has set standards for both coarse particulate matter between 2.5 and 10 micrometers in diameter (PM_{10}) and fine particulate matter with a diameter less than 2.5 micrometers ($PM_{2.5}$). For PM_{10}, which generally includes particles created by traffic-related road dust, agricultural operations, construction, industrial processes, and biomass burning, the current primary (health-based) 24-hour standard is 150 $\mu g/m^3$.[1] $PM_{2.5}$, on the other hand, can either be primary (emitted directly from sources including vehicles, smokestacks, and fires) or it can be secondary (formed when other gaseous emissions from vehicles, power plants, industry, and others react in the atmosphere). In urban areas the $PM_{2.5}$ comes predominantly from primary sources while in many rural areas secondary sources of $PM_{2.5}$ account for the majority of $PM_{2.5}$.[2] For $PM_{2.5}$ there are two primary standards including the 24-hour standard at 35 $\mu g/m^3$ and the annual standard of 12 $\mu g/m^3$.[1] Secondary standards (welfare-based) are set at the same limits as the primary standards, except for the $PM_{2.5}$ annual standard which is set at 15 $\mu g/m^3$.[1]

Across the spectrum of PM size, the scientific evidence for a relationship between PM exposure and adverse health effects is strongest for $PM_{2.5}$ with various levels of

causality determinations for multiple adverse health effects including respiratory, cardiovascular, metabolic, nervous system, reproductive and developmental, cancer, as well as increased mortality - all linked by research to $PM_{2.5.}$ The most recent Integrated Science Assessment for Particulate Matter (ISA for PM), completed in 2019, concluded that there is a causal relationship determination between both short and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality.[2] These finding were based on epidemiological studies that consistently showed positive associations between exposure and increased admissions to emergency departments and hospitalizations for ischemic heart disease, heart failure, and cardiovascular mortality as well as results from controlled human exposure studies and animal toxicological studies which provided biological plausibility including endothelial dysfunction, increases in blood pressure, and conduction abnormalities. [2]

The EPA does not include information on many specific cardiac conditions which could have a link to $PM_{2.5}$ exposure including the many types of cardiomyopathy. Figure 7.1a depicts potential biological pathways through which $PM_{2.5}$ exposure could lead to heart failure and cardiomyopathy. $PM_{2.5}$ exposure can lead to systemic oxidative stress as well as an imbalance in the autonomic nervous system. These physiological changes affect multiple factors including endothelial function, blood pressure, cardiac output, and heart rate, which can contribute to the development of cardiomyopathy and other types of heart failure.[1,3-5] One type of cardiomyopathy, peripartum cardiomyopathy (PPCM), can have a profound effect on women of child-bearing age. PPCM is a form of heart failure with no known cause that occurs towards the end of pregnancy or in the months following pregnancy in previously healthy young women where the outcomes vary from complete

recovery to persistent dysfunction, transplant, and death.[6] The cause of PPCM is not fully understood but is most likely multi-factorial with research suggesting that hormones of late pregnancy cause a vasculotoxic environment that in susceptible women leads to the development of PPCM. Hypertensive disease of pregnancy (HDP), one of the biggest known risk factors for PPCM, has been found to be related to air pollution exposure including $PM_{2.5}$.[7-12] However, as far as we know no one has studied the possibility of a relationship between $PM_{2.5}$ exposure and the development of PPCM.

We postulate that $PM_{2.5}$ exposure could increase susceptibility to PPCM in some women. Figure 7.1b depicts a model of how $PM_{2.5}$ exposure could increase susceptibility to PPCM by promoting oxidative stress and endothelial dysfunction. In this case study, we examine the ability of three commonly available methodologies (air monitoring, traffic density, and distance to major roadways) to ascertain the role of $PM_{2.5}$ exposure on a population level cohort of patients with PPCM from the federally funded Rochester Epidemiology Project (REP).[13-17] We further highlight issues preventing each method from being fully applied to understand the relationship of $PM_{2.5}$ exposure the development of PPCM. We then make policy-based recommendations that would allow studies to successfully determine whether $PM_{2.5}$ exposure leads to increased susceptibility to developing PPCM as well as related recommendations, such as including additional health endpoints like hypertensive disease of pregnancy, cardiomyopathy, and PPCM, that would lead to strengthening the human health protection required by the CAA.

Case Study

Materials and Methods

Human Subjects

The project was approved by both the Mayo Clinic and Olmsted Medical Center Institutional Review Boards and conformed to the principles set forth in the Declaration of Helsinki 1975, as revised in 2013. All patients involved in the study provided written informed consent to allow the use of their medical records for research purposes as part of the Rochester Epidemiology Project. Patients who had not previously consented to participate in research through the REP were excluded from the study.

Study Population

The study population has been described in detail previously.[18] Briefly, this study utilized data from the Rochester Epidemiology Project[13-17,19] identifying women diagnosed with PPCM (cases) and controls matched on a 2:1 basis by age, race and number of babies born during the index pregnancy (pregnancy related to initial PPCM diagnosis) for cases and the matched pregnancy in each control. We geocoded residential addresses, at time of diagnosis for cases and time of matched delivery for controls.[ii] We could not geocode the addresses for 2 cases and 1 control as the addresses could not be located on current maps.

[ii] using ArcGIS World Geocoding Service in ArcGIS Pro 2.6.0 (ESRI, Redlands, CA)

Exposure Estimates

In this case study we examined three methods of estimating exposure to $PM_{2.5}$ including EPA air monitoring data as a direct measure of $PM_{2.5}$ as well as traffic density and distance to major roadway as surrogate measures for traffic related $PM_{2.5}$ exposure.

Results

Part I: Air Monitoring

Data for location of air monitors was obtained from the Air Quality System (AQS) Monitoring Network, EPA OAR OAQPS. [iii] There are 129 AQS $PM_{2.5}$ monitors located at 87 unique sites in or around the 27-county study area that are or were active during the study time frame of 1970 to 2014. (Figure 7.2a) The residential addresses of the women in this study are shown in Figure 7.2 as dark stars for cases and light stars for controls. Initially, ArcGIS Near tool was used to identify the closest monitor to each geocoded residential address. Analysis of the near data showed that all subjects with mappable residential addresses were closest to one of 11 monitors at 9 unique locations within the region of the REP (which incorporates an area of southeastern Minnesota and southwestern Wisconsin) (Table 7.1). However, as seen in Figure 7.2 and based on AQS data the dates each monitor was active varies greatly and the monitor location closest to each residential address might not have been collecting data at the time of interest (i.e., date of PPCM diagnosis for cases or delivery date of index pregnancy for controls).

[iii]Information at: https://edg.epa.gov/metadata/catalog/search/resource/details.page?uuid=%7B7BF467D5-A5D7-427B-B896-5674A15B55B4%7D Data retrieved from: https://www.epa.gov/outdoor-air-quality-data/interactive-map-air-quality-monitors and https://gispub.epa.gov/arcgis/rest/services/OAR_OAQPS/AQSmonitor_sites/MapServer

The next step was to match each case and control to the nearest monitor that was active at the time of interest for each woman in the study. The AcrGIS Near Table Tool was used to identify the 10 closest monitors in order of increasing distance (i.e., straight line distance) to each geocoded residential address. Microsoft Excel and StataIC 15. 21 were used to identify the closest monitor that was active as the time of interest (diagnosis for cases and delivery of index pregnancy for controls). This resulted in matches for 120 women's addresses to 17 monitors in 15 unique locations (Table 7.1). The remaining 24 women could not be matched to active monitors as the times of interest for each of these women occurred between 1971 to 1997, before the first monitors in this area were active on 4/4/1997 (Figure 7.3 and Table 7.1). The locations of the 19 monitors used for the two types of matching in this study are shown in Figure 7.2b. The parameters for each of these monitors are listed in Table 7.1, and the active date range for each of the monitors is depicted visually in Figure 7.3. Continuous data are presented as median (interquartile range (IQR)). To compare cases and controls the Mann-Whitney U Test for non-normally distributed data was applied. A p value <0.05 was considered statistically significant. Data were analyzed using StataIC 15. 21. For the 120 women with date matched monitors, the distance from residential address to monitor ranged from 0.3 – 405.1 km with a median distance of 10.0 km (IQR 4.5 – 52.5 km). Cases median distance to date matched monitors was significantly further than the median distance for controls (42.9 vs 8.6 km, $p = 0.01$). (Table 7.2) However, the range of distances for controls was larger (0.85 – 103.0 km for cases vs 0.3-405.1 km for controls) with controls living up to 405.1 km from the nearest active monitor due to the locations of the only active monitors in the early years of monitoring (Table 7.2, Figure 7.2b, and Figure 7.3).

Studies on the relationship between exposure to $PM_{2.5}$ and hypertensive disorders of pregnancy use varying distances from EPA monitors from subject's residential address varying from 5 km to 20 km with one study combining data from multiple monitors within 50 km.[20-24] Studies on the relationship between $PM_{2.5}$ and heart failure or heart disease use similar distance ranges, but most are conducted in larger metropolitan areas and average multiple monitors together[iv], methodology that cannot be applied in a rural area. In this rural study area, the median distance to date-matched monitors was 10km, but distances were as large as 103 km for cases and 405 km for controls (Table 7.2). In addition, for many data points with large distances the location of the monitor was not environmentally similar the location of the subject's residence. For example, some rural residential addresses matched by date to monitors in urban Milwaukee, WI. The use of these data would likely lead to misclassification bias and possibly shift the study results towards the null.

In addition, due to the matching design of the cohort used for this study, matched pairs must be dropped from the analysis if they are missing exposure data. For this study19 case/control sets (57 women total) would need to be dropped from the analysis based on dates of interest for either the case or controls occurring before monitoring began. Due to the high number of cases and controls with no monitoring data available (40% of the cohort), analysis of $PM_{2.5}$ levels from monitoring data could not be completed for this study population.

[iv][iv] See studies included in: U.S. EPA. Integrated Science Assessment (ISA) for Particulate Matter (Final Report, Dec 2019). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-19/188, 2019.

Part II: Surrogate options

Surrogate option 1 - Distance to Major Roadway

Distance to major roadway is a commonly used surrogate for measuring air pollution exposure related to traffic. Euclidean straight-line distance to major roadway at each residential address was calculated as a proxy for traffic exposure using the NEAR function in ArcGIS. Because the study spanned a wide range of years obtaining data for each time of interest was not possible. Data for earlier years was only available as PDFs from each states Department of Transportation, and not as electronic files that could be used in ArcGIS.[v] Due to this limitation we chose to use road segments from the 2019 TIGER/line Roads National Geodatabase with exposure categories based on MAF/TIGER Feature Class Codes (MTFCC) classifications assigned by the Census Bureau.[vi,vii] (Figure 7.4). Major roadways were initially defined as those designated as MTFCC S1100 primary roadways (limited-access highways that connect to other roads only at interchanges including interstate highways and other highways with limited access). Exposure zones for traffic-related air pollution range from 50 to 1500 meters (m) from highways and major roadways with the most highly affected area occurring between 300 – 500 meters.[viii] We examined residential distance to S1100 roadways using the following cutoff points: 250 m, 500m, and 1,000m.[ix] These buffer sizes were selected based the Health Effects Institute

[v] In addition, due to COVID shutdowns and work from home orders the PDF files were not accessible during the time when this study was conducted.

[vi] 2019 TIGER/Line Shapefiles (machine readable data files) / prepared by the U.S. Census Bureau, 2019 - files and information (as well as those from other years) are available at: https://www.census.gov/geographies/mapping-files/time-series/geo/tiger-line-file.2019.html

[vii] 2019 TIGER/Line Shapefiles Technical Documentation / prepared by the U.S. Census Bureau, 2019 – see appendix E for MTFCC code definitions available at: https://www.census.gov/programs-surveys/geography/technical-documentation/complete-technical-documentation/tiger-geo-line.2019.html

[viii] Exposure zones vary by pollutant and meteorological conditions. See HEI Panel on the Health Effects of Traffic Related Pollution. 2010. Traffic-Related Air Pollution: A Critical Reivew of the Literature on Emissions, Exposures, and Health Effects. HEI Special Report 17. Available at www.healtheffects.org

[ix] Cutpoint chosen based on HEI Special report 17 cited above and review of previous studies

(HEI) report,[25] distance used in previously published studies of hypertensive disease of pregnancy[26-28] or heart disease,[29] and the information that $PM_{2.5}$ concentration appears to reach background levels around 900 meters from roadways.[30] To compare cases and controls, Chi-squared (X^2) or Fisher's exact test were used to evaluate categorical variables. A p value <0.05 was considered statistically significant. Categorical data are presented as frequency (n) and percent (%). Data were analyzed using StataIC 15.[31]

The initial analysis, using the standard definition of major roadway as those roads classified as MTFCC S1100, did not show any significant difference in distance from residential address to major roadway between cases and controls and the diagnosis of PPCM for any of the chosen buffer sizes (Table 7.3). However, it is difficult to draw conclusions based on these results as the number of study subjects that lived within any buffered distance of MTFCC S1100 roadways is very small due to the rural location of the study which contains very few roadways with this classification (Figure 7.4 and Table 7.3).

Considering the predominantly rural geography of the study area we also conducted a separate analysis where major roadways were defined as those designated as MTFCC S1100 or MTFCC S1200 secondary roadways (main arteries that are not limited access, generally U.S. highway, state highway, or county highway systems). Figure 7.4 shows the locations of MTFCC S1100 and S1200 designated roads in and near the study area. Using this broader definition of major roadways also did not find any association between distance to major roadway and diagnosis of PPCM (Table 7.3). The EPA defines "near a major roadway" as within 500-600 feet (about 152-183 meters).[x] Similarly, previous

[x]See: US EPA Office of Transportation and Air Quality. Near Roadway Air Pollution and Health: Frequently Asked Questions. Document EPA-420-F-14-044. August 2014

studies which have found positive associations between distance to major roadway and various hypertensive disease of pregnancy or cardiovascular outcomes using distance between 50 – 200 meters.[26-28,32-39] In this study, less than 5% of cases and controls in this study lived within 200 meters of a major roadway. (Table 7.3). In addition, in rural areas traffic is often not the main source of particulate matter pollution.[xi] It is likely that this method may be a better surrogate in urban areas where a higher concentration of residential addressed are within 200 meters of a major roadways and traffic emissions are a bigger source of particulate matter pollution.

Surrogate Option 2 - Traffic Density / Annual Average Daily Traffic (AADT)

Annual Average Daily Traffic (AADT) is an estimate of the total number of vehicles using a section of roadway (in both directions) on any given day of the year.[xii] AADT is a commonly used surrogate for traffic-related air pollution exposure. [26,27,33,40-47] A review of air pollution measurement methods suggests that traffic density measured at a specific location could possibly be a more accurate measure than centrally monitored air pollution, especially when the central monitors are located further from the address of interest,[29] a concern in this predominantly rural study area, as shown in the distance to monitor results in part I of this case study. As with distance to major roadway, because the study spanned a wide range of years obtaining data for each time of interest was not possible. Data for earlier years would only be availed as PDFs and not as electronic files that could be used in ArcGIS. In addition, data specific to time of pregnancy/diagnoses was

[xi] In rural areas, such as in this study, sources of air pollution differ from urban areas with traffic generally playing less of a role and additional sources including agriculture and residential wood burning playing larger roles. For example, in Minnesota – the largest source of directly emitted from combustion sources comes from residential wood burning.[40]

[xii] Further information on AADT and how it's measured and calculated can be found at the Minnesota Department of Transportation website https://www.dot.state.mn.us/traffic/data/coll-methods.html#TVP.

not available as traffic counts are conducted in cycles where either 1/3 of roadway sections are counted every 3 years or where 1/6 of roadway sections are counted every 6 years.[xiii].Due to this limitation we chose to use AADT data from the 2018 Highway Performance Monitoring System Public Release data from the U.S., the most recent year of data available, from the Department of Transportation Federal Highway Administrations Office of Highway Policy Information.[xiv]

In this study we examined AADT both as a continuous variable and as a categorical variable using the volume group /AADT ranges defined by The U.S. Department of Transportation Federal Highway Administrations Office of Highway Policy Information[xv] which are shown in Table 7.4. We also examined these data using the U.S. Department of Transportation designated cut point of 125,000 vehicles per day to define a major roadway.[xvi] To compare cases and controls Wilcoxon rank sum test was used for the analysis where AADT was treated as a continuous variable and Fisher's exact test was used for the analysis where AADT was treated as a categorical variable. A p value <0.05 was considered statistically significant. Categorical data are presented as frequency (n) and percent (%) and numeric data as median (interquartile range) for non-normally distributed data, unless otherwise specified. Data were analyzed using StataIC 15.[31]

[xiii] In addition, also only some are Continuous Counts Stations (CCS) with 24/7 traffic counting 365 days of the year at a limited number of locations. The rest are called short term counts – 48-hour counts (2 full 24-hour days) are required for HPMS data and then have calculations are done using the CCS data to covert the counts to AADT. See: U.S. Department of Transportation Federal Highway Administration Office of Highway Policy Highway Performance Monitoring System Field Manual (Dec 2016) sections 4-51 to 4-52 and 5-3 to 5-8. Available at: https://www.fhwa.dot.gov/policyinformation/hpms/fieldmanual/hpms_field_manual_dec2016.pdf

[xiv] Dataset is HPMS ARNOLD 2018 HPMS Public Release from the U.S. Department of Transportation Federal Highway Administration Office of Highway Policy. Data available at https://www.fhwa.dot.gov/policyinformation/hpms/shapefiles.cfm

[xv] See U.S. Department of Transportation Federal Highway Administration Office of Highway Policy Highway Performance Monitoring System Field Manual (Dec 2016) available at: https://www.fhwa.dot.gov/policyinformation/hpms/fieldmanual/hpms_field_manual_dec2016.pdf

[xvi] More information available at: https://www.transportation.gov/mission/health/proximity-major-roadways

ArcGIS Pro was used to create multiple ring buffers around each residential address to identify the roadway section with the highest AADT within each buffer distance. The same distances were used and chosen for the same reasons as those used for distance from major roadway in part II of this case study which included buffers of 100, 250, 500, and 1,000 meters. Figure 7.5 shows the traffic density data used for this study with Figure 7.5a depicting traffic density data in and around the study area and Figure 7.5b illustrating that that there are no road segments with AADT volume of 125,000 cars or higher within the study area. We first examined traffic density as a continuous variable with results shown in Table 7.5. The median AADT appeared to increase with increasing buffer size in both the cases and controls (Table 7.5). Contrary to our hypothesis, our results suggest that controls live near roads with higher traffic density then cases, although this difference was only significant using a 1000m buffer (Table 7.5). There are many limitations to these data. As mentioned in the methods, we could not obtain data specific to the time of interest for each case or control. In addition, states are not required to report section level AADT for all roads[xvii] and, in this rural area, when using smaller buffer sizes, we found that many study participants had no road segments with recorded AADT data with the selected buffers making it hard to draw any conclusion from the 100m and 250m buffer data (Table 7.5). At 500m and 1000m most participants had data available for analysis, but the same issues related timing of data used and frequency of actual collection (as noted in methods) applies to these results as well.

[xvii] States are not required to report section level AADT for non-Federal-Aid, non-NHS (National Highway Safety System) roadways so AADT for every road is not available (generally this includes only smaller roads – minor collectors and local roads) p 1-3 table 1.1 of the U.S. Deptment of Transportation Federal Highway Administration Office of Highway Policy Highway Performance Monitoring System Field Manual (Dec 2016) available at: https://www.fhwa.dot.gov/policyinformation/hpms/fieldmanual/hpms_field_manual_dec2016.pdf

Results treating AADT as a categorical variable are shown in Table 7.6. There were no significant relationships between highest AADT level and diagnosis of PPCM at any buffer distance examined. However, most of the higher AADT volume groups, which are the ones usually considered as significant exposures, have no or very low values as this rural study area does not have roads with these higher levels of traffic (Figure 7.5, Table 7.6). Due to the lack of participants living near high traffic density roads it is hard to draw any conclusions from these findings.

Discussion and Policy Recommendations

The Rochester Epidemiology Project is a collaboration of health care providers in southeast Minnesota and Southwest Wisconsin sharing medical information with researchers by linking medical records data together allowing for population-based research can be conducted.[13-17,19] The design of the Rochester Epidemiology Project (REP) provides a rare opportunity to study relationships between environmental exposures, such as air pollution, and disease outcomes at a population level with increased generalizability compared to single center or multi-center cohort studies. However, as this case study demonstrates, this federally funded, potentially high impact resource, cannot currently be leveraged to study the effect of air pollution on health outcomes, such as PPCM, primarily because of the lack of pollution monitors in this rural region of the U.S. Below we will discuss the issues identified through this case study and make policy recommendations that could address these issues to improve the ability of future research to undertake exposure studies using the REP. Addressing these limitations would also ultimately improve the health protection that is required by the CAA.

Data limitations prevented the full application and analysis of all three of the currently available methods to assess $PM_{2.5}$ exposure examined in this case study. Of the three approaches air pollution monitors are the preferred method to determine this relationship as the monitors measure ambient levels of pollution accounting for all sources, which is particularly important in rural areas where traffic may not be the primary source of $PM_{2.5}$. However, monitoring networks in the U.S. generally focus on areas with high population density and have minimal resources (i.e., few monitors) in rural areas, which makes it difficult to use monitoring data to measures health effects of pollution exposure in rural areas, such as in this case study. Because direct exposure could not be measured using air monitoring data for this study, we examined two commonly used surrogate measures; distance to major roadway and traffic density as other means to measure the effect of $PM_{2.5}$ exposure on the development of PPCM in this population. The biggest limitation to both of these methods is that they are surrogate measures for traffic-related pollution and do not take into account other sources of $PM_{2.5}$ in the environment, which in rural areas (such as this study location) may contribute more to $PM_{2.5}$ than traffic such as agricultural sources and residential woodburning.[xviii] However, it was important to examine these surrogates, despite this their limitations, to determine if they could measure $PM_{2.5}$ exposure and its potential effect on the development of PPCM. However, neither of these surrogate measures led to useable results. We found that the cases and controls in this case study lived in rural areas with smaller roads, lower traffic density, and this likely related to lower traffic emissions. Thus, traffic-related pollution is not likely to be a major source of

[xviii] In rural areas, such as the area of this case study, sources of air pollution differ from urban areas with traffic generally playing less of a role and additional sources including agriculture and residential wood burning playing larger roles. For example, in Minnesota – the largest source of directly emitted from combustion sources comes from residential wood burning. See Smith, AJ. et al., The air we breathe the state of Minnesota's air quality 2019. Minnesota Pollution Control Agency (2019).

$PM_{2.5}$ exposure for this study population. In rural areas, such as the REP region used in this study, monitoring data would provide the most accurate measure as it would account for all sources of $PM_{2.5}$ levels including agriculture and residential woodburning, key contributors in rural areas. However, as this case study shows, current monitoring is not sufficient to assess health effects due to too few monitors for $PM_{2.5}$ in this rural area. Below we present four policy recommendations to address this gap that could improve understanding of the role of $PM_{2.5}$ on adverse health outcomes, such as PPCM, as examined in this study.

1. Design monitoring with research in mind

The CAA requires the EPA to set NAAQS to protect human health with an adequate margin of safety based on 5-year reviews of available scientific data. While the NAAQS are set based on scientific evidence reviewed in the required ISAs, the required monitoring is specifically to assess if states are meeting the NAAQS required levels. Monitoring for air pollutants, including $PM_{2.5}$, are set in the CAA.[xix] These requirements are based on population counts and on the 3-year design value for each area, whether it is ≤ or ≥ and of the $PM_{2.5}$ NAAQS values. With higher population and areas with 3-year design value ≥85% of any $PM_{2.5}$ NAAQS requiring more monitors. Providing high quality data to improve research related to the health effects of exposure is not the aim of the CAA, even though the NAAQS are set based on the results from scientific research. Monitoring should be designed and implemented with the goal of improving and increasing data available for research, not just to assess attainment. This would require a more complete network of monitoring throughout the US, including rural areas which have different sources of air

[xix] See Appendix D of 40CFR Part 58 Table B1

pollution, such as the area in this case study (the area of the REP) where monitor data could not be applied due to lack of monitoring in rural areas. The monitors currently used can effectively assess air quality, but are too distant to monitor all neighborhoods and it is possible for specific locations to not meet the NAAQS set levels even though monitoring (which may only occur at a regional level) shows that the levels of air pollution are safe. In addition, often, monitors are installed in new areas to establish if those areas are meet the NAAQS standards and if these areas meet the standards, then those monitors are often discontinued so that the resources can be focused on another area. To further research, monitors need to be continually active throughout the network. We saw in this case study that the monitors in the area were active at a range of different times (Figure 7.1 and Table 7.3) which impedes research over larger areas as well as in more rural areas. Both of these changes would increase the availability of high-quality data allowing for better studies on the health effects of $PM_{2.5}$ (and other air pollutants) which would improve the science used to set the NAAQS thereby increasing the protection of human health as required by the CAA.

2. Increased focus on non-urban areas

Monitoring and remediation generally focus on urban areas that have the highest population density, highest density of roads, highest levels of traffic, largest number of industrial air pollution sources, and highest levels of air pollution. While more people live in urban areas, the population in rural areas have demographic and economic differences from urban areas that may increase their susceptibility to the adverse health effects of air pollution. For example, using this study's geographical area, while only about 26% of MN residents live in non-urban areas, these areas have higher rates of older residents, lower

levels of education, higher rates of unemployment, lower median earnings, and higher rates of poverty.[48],[xx] Older populations are already included in the EPA's "At-Risk" classification due to a known increase risk to adverse health outcomes from exposure to air pollution including $PM_{2.5}$. However, both within Minnesota and the United States as a whole, people with lower incomes or social economic disadvantages are more likely to live in areas with air pollution levels that are above the NAAQS guidelines.[49],[xxi] In addition, non-white populations also face an increased risk of adverse effects from air pollution along with higher rates of factors such as low socioeconomic status that also increase susceptibility to adverse health effects from air pollution exposure.[xxii] In the population used for this case study, rates of PPCM were increased in non-white women and in women with lower social economic status.[18],[xxiii] These are two groups with a known increased risk for adverse health effects from air pollution exposure; however, as shown in this case study, due to the lack of focus on monitoring in rural areas the effect of air pollution on these populations cannot be studied effectively.

3. Add pregnant women to the list of "at-risk" populations

NAAQS are intended to "Accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in the ambient air." [xxiv] However, the

[xx]See: Rural Health Information Hub. Minnesota State Guide. https://www.ruralhealthinfo.org/states/minnesota. Last updated 1/22/2019. Last accessed 2/20/2021

[xxi] See: Minnesota Pollution Control Agency. Disproportionate impacts in Minnesota. Available at: https://www.pca.state.mn.us/air/disproportionate-impacts-minnesota. Last accessed 2/20/2021.

[xxii] For more information see the website: Dispariaties in the Impact of Air Polltion from the American Lung Association available at: https://www.lung.org/clean-air/outdoors/who-is-at-risk/disparities

[xxiii] Using medical assistance as a surrogate for social economic status. See ref 18.

[xxiv]CAA – 42 U.S.C. 7408(a)(2)

EPA does not include pregnant women in the "At-Risk Populations" under the CAA.[50,] A recent study presents a clear case for including pregnant women in this classification based on associations of hypertensive diseases of pregnancy(HDP), one of the biggest risk factors for PPCM, and air pollution.[12] HDP is a leading cause of maternal morbidity and mortality during the perinatal period leading to disease and death in young women. In addition, the development of HDP is associated with exposure to air pollution.[7-12] In the 2019 ISA for PM the EPA acknowledged for the first time that $PM_{2.5}$ exposure during the perinatal period may affect maternal health during pregnancy, including contributing to the development of HDP.[2],[xxv] Exposure to air pollution, including $PM_{2.5}$, is associated with adverse birth outcomes, including low birth weight, preterm birth, and still birth.[51] More research is needed into emerging adverse health outcomes, including HDP and PPCM, to further support the importance including pregnant women as a susceptible group. The addition of maternal health endpoints in the ISA for PM (and other air pollutants) could help guide the CAA reviews and ultimately strengthen the protection from NAAQS standards for this very large group of particularly vulnerable young women.

4. Increased funding

Significant changes to the current monitoring system and resulting data cannot be made without sufficient funding in place to continually support them. Funding needs to be secured for increased monitoring, handling and analyzing the data, grants to support the

[xxv] On page 9-11 and in figure 9-2 of the 2019 ISA for PM the EPA notes that $PM_{2.5}$ exposure may contribute to adverse events during pregnancy like HDP but do not consider these as specific health endpoints – only as steps within the presented plausible biological pathways leading to the adverse birth outcome endpoints. U.S. EPA. Integrated Science Assessment (ISA) for Particulate Matter (Final Report, Dec 2019). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-19/188, 2019.

state and local governments designing and implementing the monitoring, and to fund research with the resulting improved data. One of the main funding sources for monitoring comes from federal grants and matched state funds. However, in recent years congress has repeatedly tried to reduce the funding designated for state and local air quality grants.[xxvi] Without sufficient funding the available monitoring data will continue to be insufficient for high quality research into the health effect of air pollution exposure. In the most recent ISA for PM the EPA notes that research into many health effects is limited and that more data are needed. Without improved data the EPA cannot complete its duty of "…protecting human health with an adequate margin of safety…" one of the key requirements of the CAA. New funding will need to be designated, above what is currently in place, for real, significant changes to be made.

Conclusions

In this case study we attempted to determine whether exposure to $PM_{2.5}$ contributes to the development on PPCM in a population level cohort using the Rochester Epidemiology Project employing three commonly used methods to measure pollution exposure: monitoring, distance to major roadway, and traffic density. However, we found that in the rural area where the study and control cohort lived the current monitoring network was not sufficient to measure the effect of $PM_{2.5}$ exposure on adverse health outcomes for PPCM. Additionally, surrogate methods for exposure to $PM_{2.5}$ based on traffic-based measures did not find a relationship between $PM_{2.5}$ and increase diagnosis of PPCM. This may be due however to these measures not being suitable in rural areas due to

[xxvi]While they have not been successful in the last few years, for fiscal years 2019, 2020, and 20121 they tried to decrease the budget for air grants by about $76 million (about 33%) each year. More detail can be found on the National Associations of Clean Air Agencies website under its appropriation section at: http://www.4cleanair.org/happening-in-congress/category/appropriations.

the predominant sources of or $PM_{2.5}$ coming from non-traffic related sources such as agriculture. The CAA requires the EPA to establish science-based exposure standards for $PM_{2.5}$ and other air pollutants (NAAQS standards) to protect public health with an adequate margin of safety. The most recent ISA for PM concludes that there is a casual relationship between $PM_{2.5}$ and specific cardiovascular health effects based on the currently available scientific data. However, data are lacking for the relationship between $PM_{2.5}$ and PPCM. This omission leaves women of reproductive age, a large population that is potentially more susceptible particularly during pregnancy, out of the considerations used in setting the NAAQS required by the CAA. A monitoring system driven by scientific needs, increased focus on rural areas, an inclusion of pregnant women in the "at-risk" designation, and increased funding to support each of these items are needed to strengthen human health protection from $PM_{2.5}$ as required by in the CAA.

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Table 7.1 Monitor parameters for the 19 monitors included in this study.

Closest Match	Date Match	AQS Site ID	City	State	Monitor Start Date	Last Sample Date	Measurement Scale Definition	Sampling Duration	Sample Collection Frequency
	✓	55-079-0010	Milwaukee	WI	4/4/1997	10/2/1998	4 km to 50 km	24 hours	Every 6th day
	✓	55-055-0008	Waterloo	WI	1/1/1999	3/4/2003	100 m to 500 m	24 hours	Every 3rd day
✓	✓	27-037-6018	Hastings	MN	4/24/1999	12/29/2003	4 km to 50 km	24 hours	Every 3rd day
	✓	19-033-0019	Mason City	IA	7/1/1999	8/4/2004	missing	24 hours	Every 3rd day
✓	✓	27-047-5401	Albert Lea	MN	10/1/1999	6/30/2001	4 km to 50 km	24 hours	Every 6th day
✓	✓	19-063-0003	Estherville	IA	1/1/2000	12/29/2004	missing	24 hours	Every 3rd day
	✓	27-139-0505	Shakopee	MN	1/1/2000	7/22/2018	500 m to 4 km	24 hours	Every 3rd day
✓	✓	27-109-5008	Rochester 1	MN	1/7/2000	6/29/2019	500 m to 4 km	24 hours	Every 3rd day
	✓	27-037-0470	Apple Valley	MN	10/3/2000	6/29/2019	500 m to 4 km	24 hours	Every 3rd day
✓		27-103-5109	N. Mankato	MN	10/3/2000	9/10/2001	missing	24 hours	Every 6th day
	✓	19-147-1002	Emmetsburg	IA	1/1/2005	6/29/2020	50 to hundreds km	24 hours	Every 3rd day
✓	✓	55-063-0012	La Crosse 1	WI	12/7/2005	3/27/2018	50 to hundreds km	24 hours	Every 6th day
	✓	27-163-0446	Bayport	MN	5/17/2007	12/27/2009	100 m to 500 m	24 hours	Every 6th day
✓	✓	55-035-0100	Eau Claire 1	WI	3/17/2009	3/28/2011	4 km to 50 km	24 hours	Every 6th day
✓	✓	55-063-0012	La Crosse 2	WI	7/14/2010	3/31/2020	50 to hundreds km	1 hour	Daily
✓	✓	27-109-5008	Rochester 2	MN	1/1/2011	3/31/2020	500 m to 4 km	1 hour	Daily
	✓	55-035-0014	Eau Claire 2	WI	4/1/2011	3/27/2018	50 to hundreds km	24 hours	Every 6th day
✓		27-169-5220	Winona	MN	1/1/2014	12/31/2014	500 m to 4 km	1 hour	Daily
	✓	27-037-0480	Lakeville	MN	1/1/2015	3/31/2020	100 m to 500 m	1 hour	Daily

Table 7.2. Distance to monitor matched using date of interest

	All (*n* = 120)	Cases (*n* = 43)	Controls (*n* = 77)	*p* value
Median (IQR)	10.0 (4.5 – 52.5)	42.9 (5.9 – 63.7)	8.6 (4.1 – 29.0)	0.01
Range	0.3 – 405.1	0.85 – 103.0	0.3 – 405.1	

Table 7.3 $PM_{2.5}$ exposure from traffic using distance to major roadway as a proxy for traffic exposure.

Category[a]	Distance (m)	Cases n (%)	Controls n (%)	*p* value
S1100 Primary Roads[b,c]	< 250	2 (4%)	3 (3%)	0.66
	< 500	3 (7%)	12 (13%)	0.39
	< 1000	7 (15%)	23 (24%)	0.28
S1100 Primary & S1200 Secondary Roads[b,c,d]				
	< 250	11 (24%)	17 (18%)	0.40
	< 500	16 (35%)	40 (42%)	0.40
	< 1000	32 (70%)	70 (75%)	0.61

[a] Exposure categories are based on MTFCC classifications and data is from the 2019 TIGER/line Roads National Geodatabase. Source for exposure categories: 2019 TIGER/Line Shapefiles Technical Documentation prepared by the U.S. Census Bureau, 2019 – see appendix E for MTFCC code definitions available at: https://www.census.gov/programs-surveys/geography/technical-documentation/complete-technical-documentation/tiger-geo-line.2019.html

[b] 2 cases and 1 control are not included because addresses could not be mapped.

[c] S1100 Primary roads include interstate highways and all other highways with limited access (connecting to other roads only at interchanges and not at-grade intersections).

[d] S1200 Secondary Roads are main arterials that are not limited access (usually connect to many other roads with at-grade intersections) including U.S. highways, state highways, county highways.

Abbreviations: MAF/TIGER Feature Class Codes, MTFCCC; $PM_{2.5}$, fine particulate matter with diameter less than 2.5 micrometers

Table 7.4. AADT Volume Groups[a]

Group	AADT Volume
1	Under 500
2	500 - 1,999
3	2,000 - 4,999
4	5,000 - 9,999
5	10,000 - 19,999
6	20,000 - 34,999
7	35,000 - 54,999
8	55,000 - 84,999
9	85,000 - 124,999
10	125,000 - 174,999
11	175,000 - 249,999
12	250,000 and more

[a]Source: U.S. Department of Transportation Federal Highway Administration Office of Highway Policy Highway Performance Monitoring System Field Manual (Dec 2016) sections 4-51 to 4-52 and 5-3 to 5-8. Available at: https://www.fhwa.dot.gov/policyinformation/hpms/fieldmanual/hpms_field_manual_dec2016.pdf

Abbreviations: AADT – average daily traffic density

Table 7.5 Effect of traffic density by buffer size, treating AADT as a continuous variable

Buffer size (m)	Total *n*	Observations	Missing	Median	IQR	p value
100	144	47	97	8,031	2,471 – 11,896	0.24
250	144	98	46	8,348	4,200 – 12,921	0.08
500	144	127	17	9,700	4,700 – 20,233	0.38
1,000	144	135	9	16,900	9,000 – 27,176	0.04*

Abbreviations: AADT – average daily traffic density

Table 7.6 Effect of traffic density by buffer size, treating AADT as a categorical variable

Group	AADT Volume	100 m Cases (*n*=48)	100 m Controls (*n*=96)	250 m Cases (*n*=48)	250 m Controls (*n*=96)	500 m Cases (*n*=48)	500 m Controls (*n*=96)	1,000 m Cases (*n*=48)	1,000 m Controls (*n*=96)
1	Under 500	0 (0)	1 (1.0)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)
2	500 - 1,999	3 (6.3)	5 5.2)	3 (6.3)	6 (6.3)	4 (8.3)	6 (6.3)	3 (6.3)	3 (3.1)
3	2,000 - 4,999	4 (8.3)	3 (3.1)	12 (25.0)	7 (7.3)	7 (14.6)	19 (19.8)	5 (10.4)	10 (10.4)
4	5,000 - 9,999	3 (6.3)	12 (12.5)	9 (18.8)	24 (25.0)	10 (20.8)	18 (18.8)	8 (16.7)	11 (11.5)
5	10,000 - 19,999	3 (6.3)	8 (8.3)	7 (14.6)	14 (14.6)	11 (22.9)	19 (19.8)	12 (25.0)	24 (25.0)
6	20,000 - 34,999	0 (0)	5 (5.2)	1 (2.1)	8 (8.3)	4 (8.3)	13 (13.5)	8 (16.7)	22 (22.9)
7	35,000 - 54,999	0 (0)	0 (0)	0 (0)	1 (1.0)	0 (0)	1 (1.0)	2 (4.2)	2 (2.1)
8	55,000 - 84,999	0 (0)	0 (0)	1 (2.1)	3 (3.1)	1 (1.0)	10 (10.4)	2 (4.2)	14 (15.6)
9	85,000 - 124,999	0 (0)	0 (0)	1 (2.1)	0 (0)	2 (4.2)	2 (2.1)	2 (4.2)	7 (7.3)
10	125,000 - 174,999	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
11	175,000 - 249,999	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
12	250,000 and more	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
n/a	missing	35 (72.9)	62 (64.6)	14 (29.1)	32 (33.3)	9 (18.8)	8 (8.3)	6 (12.5)	3 (3.1)
	p value	*p* = 0.33		*p* = 0.09		*p* = 0.60		*p* = 0.50	

Abbreviations: AADT – average daily traffic density

Figure 7.1 Potential Biological Pathways for Heart Failure, Cardiomyopathy, and Peripartum Cardiomyopathy post exposure to air pollution including $PM_{2.5}$.

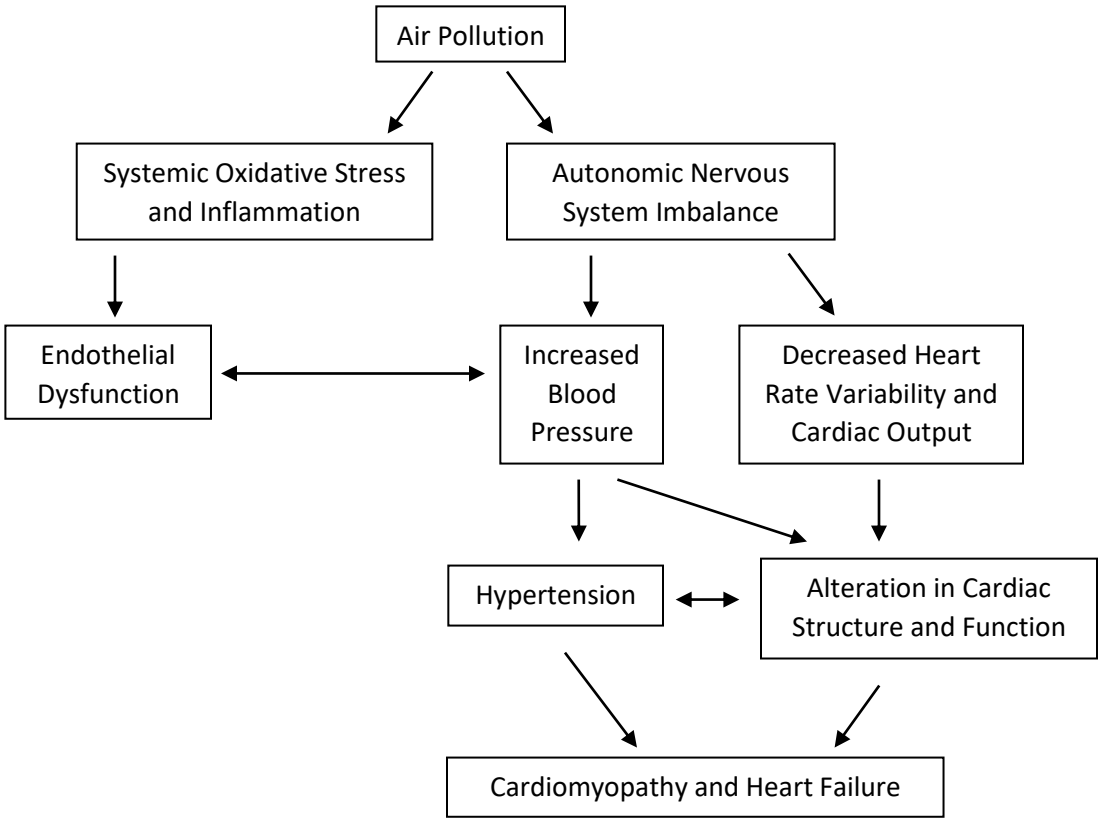

Figure 7.1a Mechanism for the role of air pollution exposure in the development of cardiomyopathy and heart failure.

Exposure to air pollution can lead to systemic oxidative stress (i.e., reactive oxygen species) as well as an imbalance in the autonomic nervous system. These physiological changes affect multiple factors including endothelial function, blood pressure, cardiac output, and heart rate, which may result in cardiomyopathy or heart failure. Abbreviations: BP, blood pressure; $PM_{2.5}$, fine particulate matter with diameter less than 2.5 micrometers Figure adapted from: Cosselman, K. E., Navas-Acien, A., & Kaufman, J. D. (2015). Environmental factors in cardiovascular disease. Nat Rev Cardiol, 12(11), 627-642. doi: 10.1038/nrcardio.2015.152

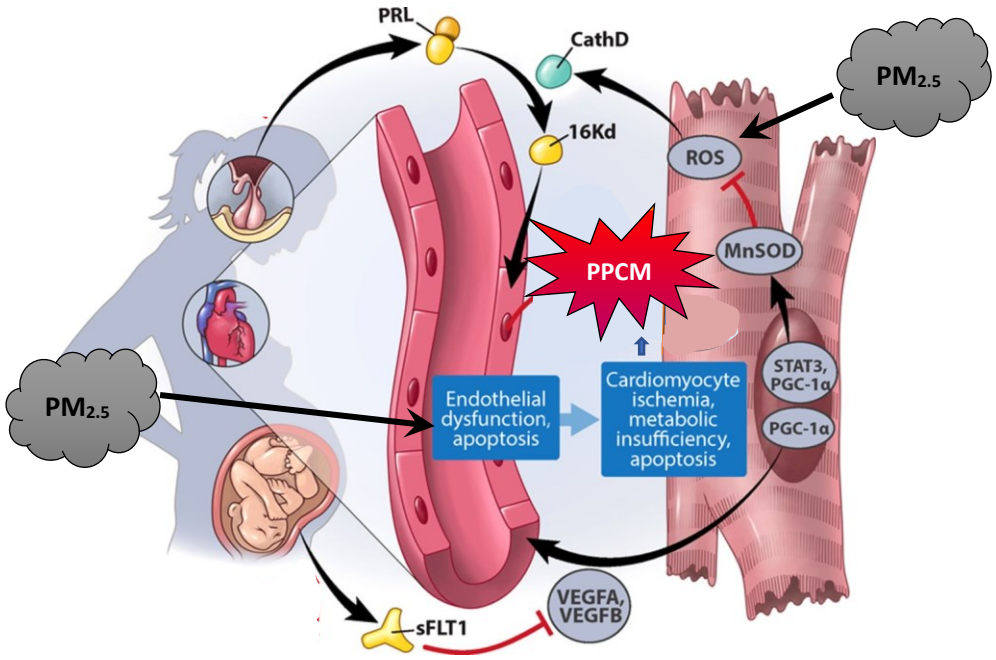

Figure 7.1b Proposed mechanism for how $PM_{2.5}$ could increase susceptibility to PPCM.

Exposure to $PM_{2.5}$ may increase oxidative stress leading to increased reactive oxygen species and / or may cause endothelial dysfunction, both of these pathways are part of the currently accepted mechanism for the development of PPCM. Abbreviations: STAT3, signal transducer and activator of transcription 3; PGC-1α, proliferator-activated receptor-gammacoactivator-1α; sFlt1, soluble Fms-like tyrosine kinase 1; 16Kd, 16-kDa form of prolactin; MnSOD, manganese superoxidedimutase; CathD, cathepsin D; PRL, prolactin; VEGF-A/B, vascular endothelial growth factors; ROS, reactive oxygen species. Figure adapted from Arany, Z., & Elkayam, U. (2016). Peripartum Cardiomyopathy. Circulation, 133(14), 1397-1409. doi: 10.1161/circulationaha.115.020491

Figure 7.2 Study area with $PM_{2.5}$ monitoring locations and residential addresses.

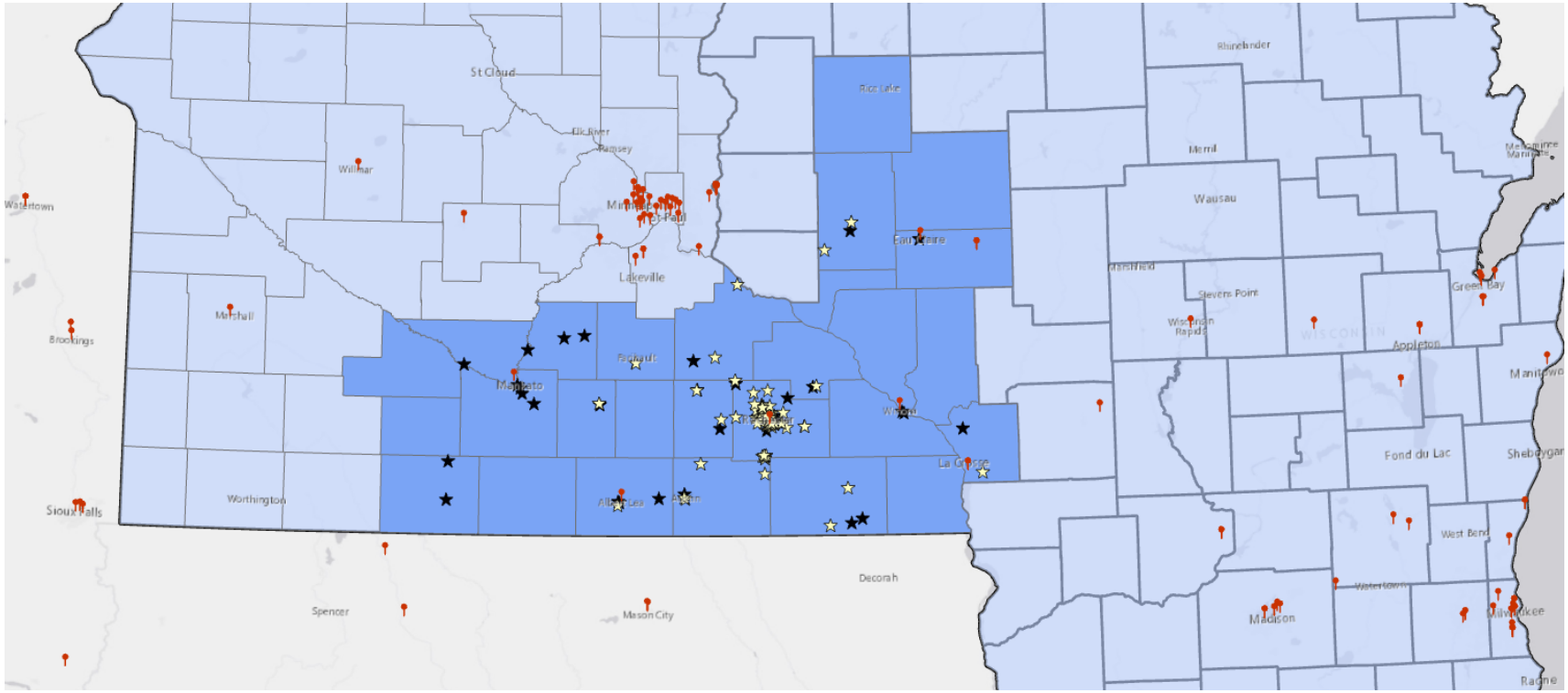

Figure 7.2a All Monitors in or around the study area.

The counties colored darker blue are the 27 counties included in the Rochester Epidemiology Project and the lighter blue are other MN or WI counties. Red push pins signify the locations of the 129 AQS $PM_{2.5}$ monitors at 87 unique sites located in or around the study area that are or have been active at any time during the study's time frame. Location of cases are indicated by dark stars and locations of controls by the light stars. Abbreviations: AQS, Air Quality System; MN, Minnesota; $PM_{2.5}$, particulate matter with diameter less than 2.5 micrometers; WI, Wisconsin.

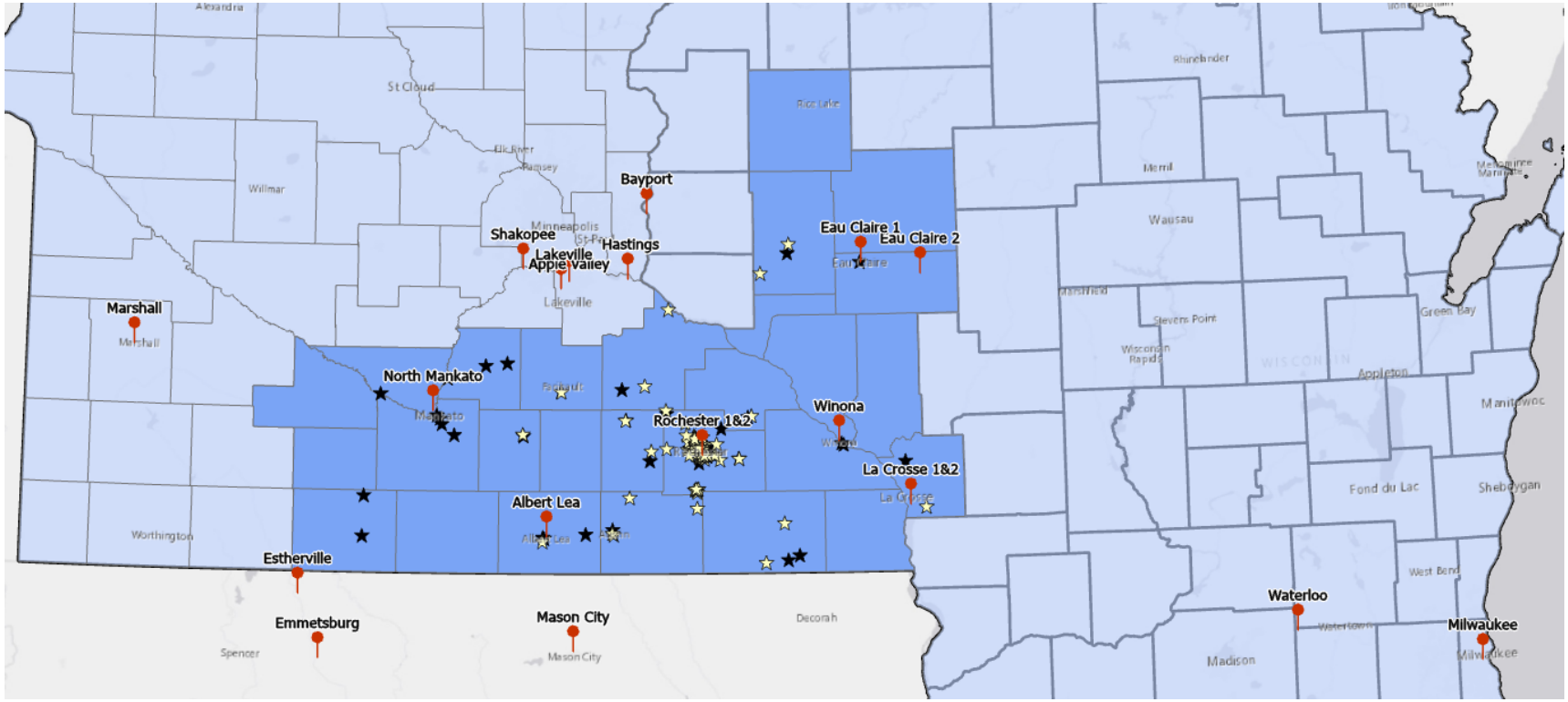

Figure 7.2b Monitors used in this study.

Locations of 19 $PM_{2.5}$ monitoring stations included in this case study are marked by red push pins. Location of cases are indicated by dark stars and locations of controls by the light stars. Monitors that are outside of the direct study area are included on the map when these monitors matched cases or controls as the "closest monitor" or "closest monitor with data from appropriate date". Abbreviations: $PM_{2.5}$, particulate matter with diameter less than 2.5 micrometers .

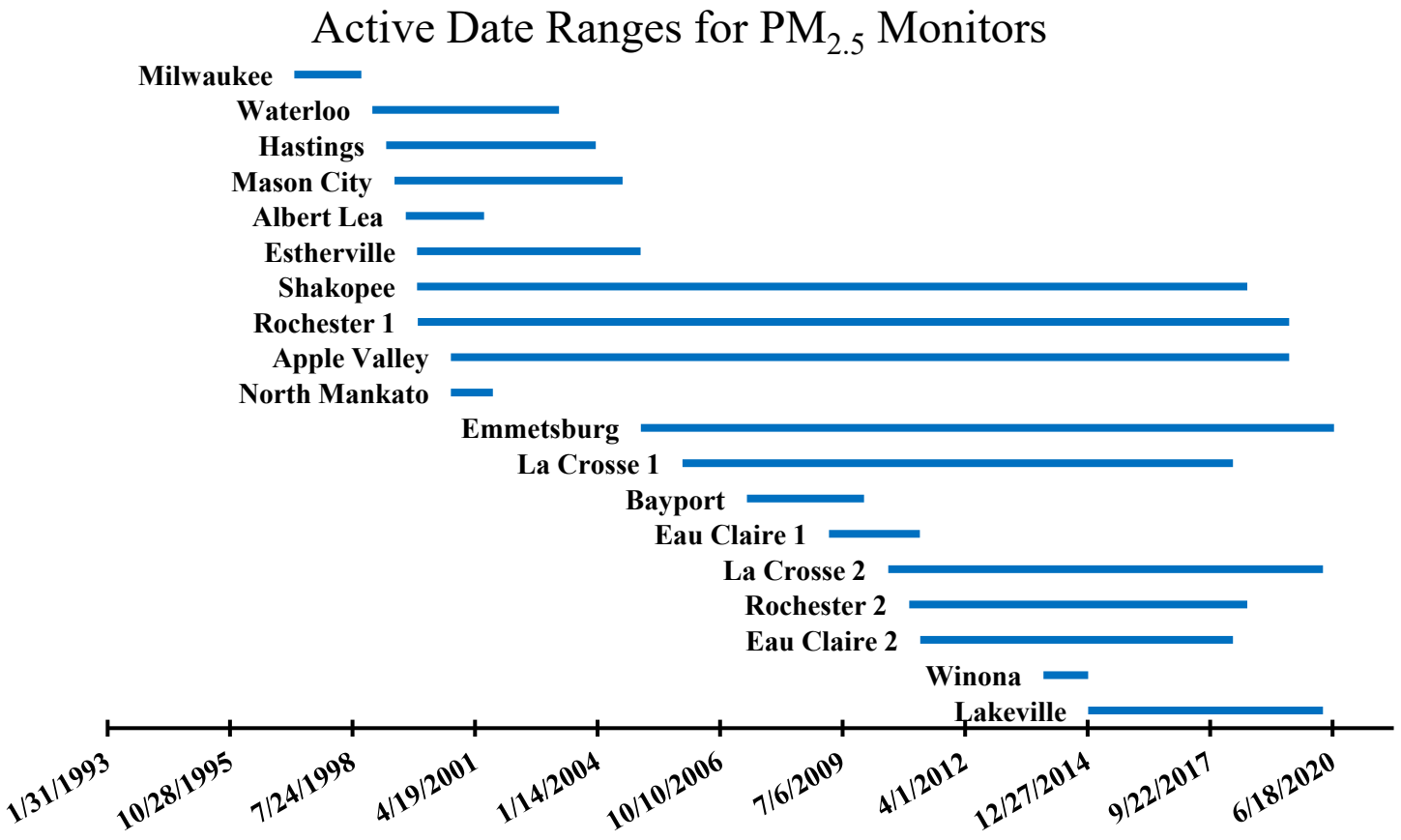

Figure 7.3 Active data ranges for each of the 19 $PM_{2.5}$ monitoring locations included in this study.

Abbreviations: $PM_{2.5}$, particulate matter with diameter less than 2.5 micro

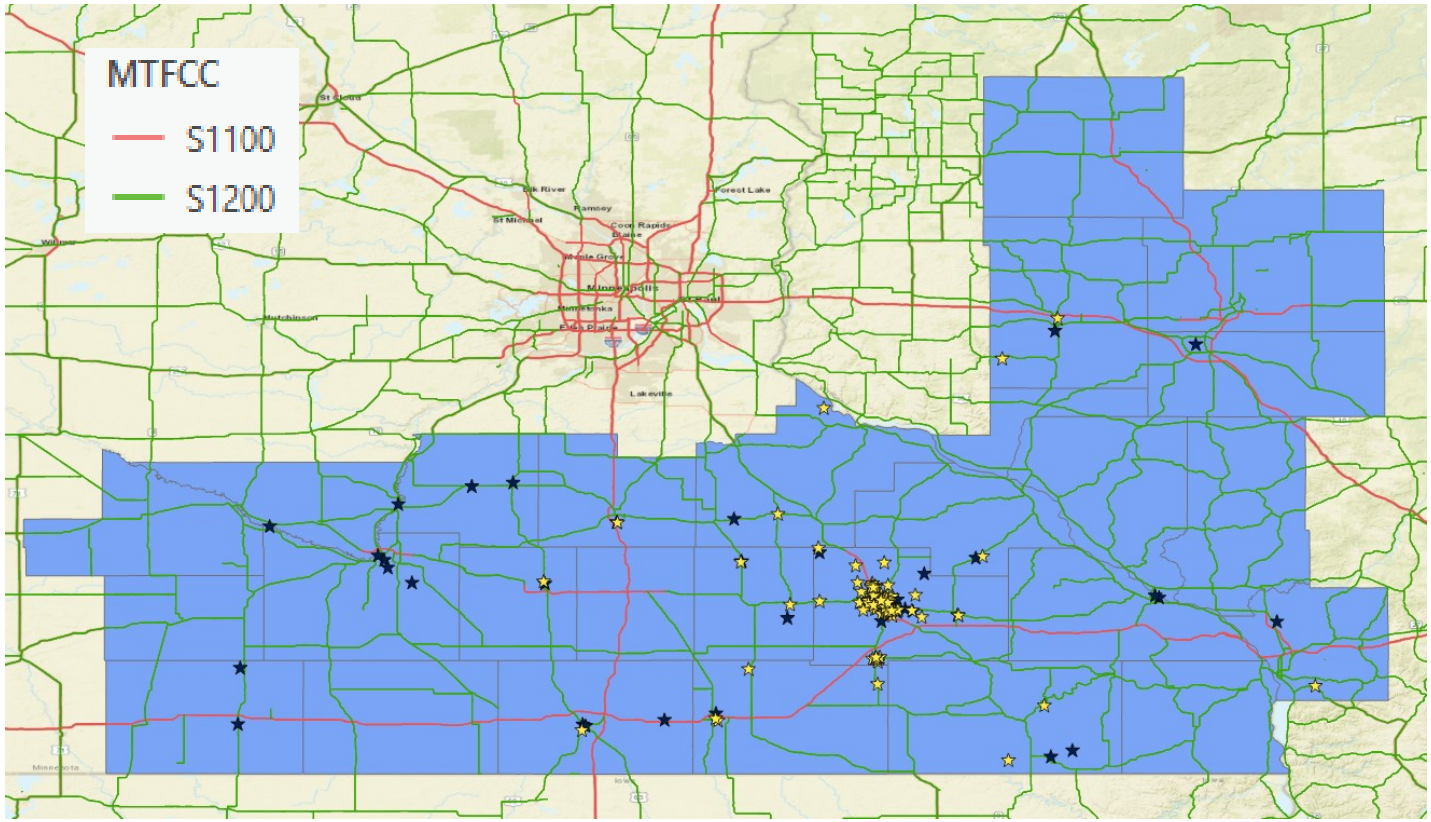

Figure 7.4 Major Roadways using MTFCC Classifications.
S1100 Primary Road Road/Path Features (Orange) are limited-access highways that connect to other roads only at interchanges and not at at-grade intersections. This category includes Interstate highways, as well as all other highways with limited access (some of which are toll roads). Limited-access highways with only one lane in each direction, as well as those that are undivided, are also included under S1100. S1200 Secondary Road Road/Path Features (green) are main arteries that are not limited access, usually in the U.S. highway, state highway, or county highway systems. These roads have one or more lanes of traffic in each direction, may or may not be divided, and usually have at-grade intersections with many other roads and driveways. They often have both a local name and a route number. Residential addresses of cases are represented by black stars and those of controls are represented by yellow stars.

Figure 7.5 Average annual daily traffic (AADT) density maps for the study area

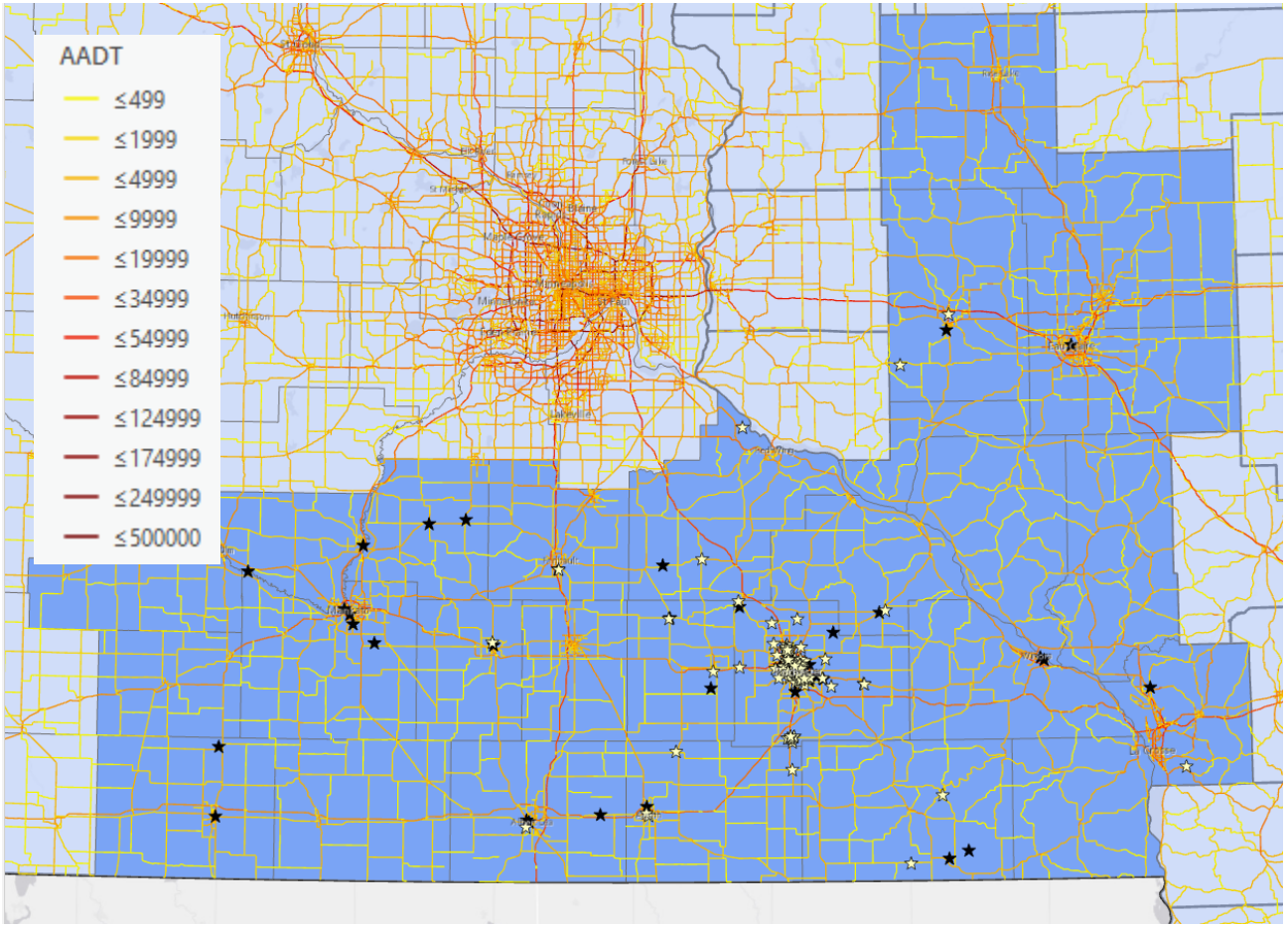

Figure 7.5a Average Annual Daily Traffic estimates for road segments in and near the study area.

Residential addresses of cases are represented by black stars and those of controls are represented by yellow stars.

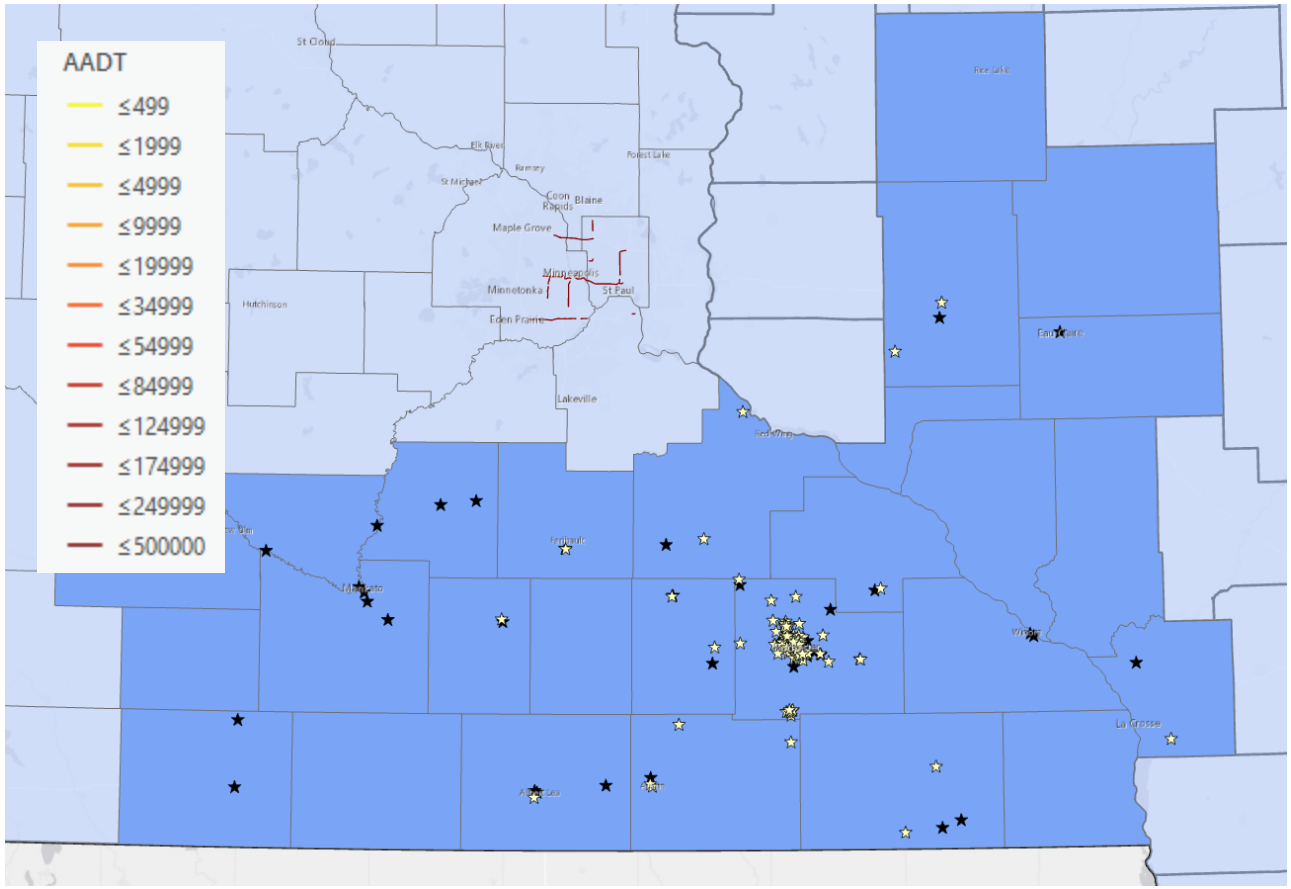

Figure 7.5b Only road segments with AADT volume of 125,000 cars or higher.

There are no road segments with average annual daily traffic (AADT) volume >125,000 with in the predominantly rural study area. Residential addresses of cases are represented by black stars and those of controls are represented by yellow stars.

Chapter 8: Conclusions

Peripartum Cardiomyopathy (PPCM) can have a profound effect on previously healthy young women as well as their families. The cause of PPCM is not fully understood, but it is most likely multifactorial and driven by a vasculotoxic environment caused by late pregnancy hormones. Susceptibility to PPCM may also be increased by other factors such as oxidative stress, inflammation, infection, and anti-angiogenic molecules. One well known environmental source of inflammation and oxidative stress that is linked to the development of multiple types of cardiovascular disease is air pollution including $PM_{2.5}$. Based on the known associations between $PM_{2.5}$ exposure and multiple types of cardiovascular disease as well as the potential mechanistic overlaps in pathophysiology we hypothesized that exposure to $PM_{2.5}$ during pregnancy and post-delivery may increase the risk of developing PPCM.

To investigate our hypothesis a case-control cohort was created using the Rochester Epidemiology Project (REP). Previous studies of PPCM either relied on diagnosis codes to identity cases or were limited to the information available in the institution(s) medical records. Using the REP as the data source for our cohort allowed us to create, to our knowledge, the first population level study of PPCM with complete medical record review to confirm diagnosis. The REP is a unique, data rich, long standing resource for conducting epidemiology studies and we envisaged leveraging all the strengths of the REP to study the relationship between exposure to $PM_{2.5}$ and the development of PPCM.

The first part of this dissertation, presented in Chapter 2, was a clinically focused literature review of PPCM including subsections on the case definition, epidemiology, pathophysiology, genetics and risk factors, diagnosis, biomarkers, treatment, outcomes, subsequent pregnancy, additional clinical concerns, knowledge gaps, and clinical care points. This manuscript was published in *Cardiology Clinics*: *Douglass EJ, Blauwet LA. Peripartum Cardiomyopathy. Cardiology Clinics 2021;39(1):119-142. DOI: 10.1016/j.ccl.2020.09.008.*

The two studies presented in Chapters 4 and 5 of this dissertation present the first, to our knowledge, population level epidemiology studies of PPCM that use complete medical record review to confirm diagnosis. After full medical record review only 55% (48/88) of women with diagnosis codes for PPCM in their medical records were confirmed to have PPCM. This result supports our decision to create a new cohort from the REP database to reduce misclassification bias in the cohort used to conduct the environmental epidemiology study proposed in Aim 2 of this dissertation.

First, we created a cohort of residents residing in Olmsted County, MN which has the most complete coverage of any county included in REP at 99.9%, with the data presented in Chapter 4. Based on this cohort of 15 women the incidence rate of PPCM in Olmsted County, MN from 1970-2014 was calculated to be 20.3 cases per 100,000 live births.[1] The women in this study had complete cardiac recovery post diagnosis. There were multiple subsequent pregnancies with a 26% relapse rate, but all of these women fully recovered with none developing persistent cardiac dysfunction or needing device therapy or transplant. Using the data from this study we identified five potential novel risk factors for PPCM including depression, anxiety, infections, migraines, and allergies. Due to the

small sample size of the Olmsted County cohort (*n*=15) we next expanded our study to the entire 27 county region of the Rochester Epidemiology Project. For the expanded study we also identified controls at a 2:1 ratio to be used for the epidemiology case-control study as well as the air pollution analysis. We matched controls on race, age, and number of babies born during the index pregnancy for a total of 48 cases and 96 controls. These results of the epidemiology study of cases and controls are presented in Chapter 5 as a manuscript that was published in the *Journal of Cardiac Failure*: *Douglass EJ, et al. A Case-Control Study of Peripartum Cardiomyopathy Using the Rochester Epidemiology Project. J Card Fail. 2021 Feb;27(2):132-142. doi: 10.1016/j.cardfail.2020.12.021. Epub 2021 Jan 1. PMID: 33388468*.

This larger epidemiology case-control study found that women with PPCM had a higher median BMI and were more likely to be overweight or obese. They were also more likely to have government-sponsored healthcare and unplanned pregnancies compared to controls who had higher rates of private insurance and planned pregnancies. As in previous studies of PPCM, hypertensive disease of pregnancy during index pregnancy was a major risk factor. The study further supports the finding that prior diagnosis of migraines ($p<0.001$) and anxiety ($p=0.03$) may be novel risk factors for PPCM. The study also found an impact on the infants born during the index pregnancies that infants born to women with PPCM had lower birth weights and were more likely to be born at an earlier gestational age (i.e., premature). The diagnosis, treatment, and outcomes of the 48 women were also presented in this manuscript with the majority (89.6%) having recovered cardiac function, with only 1 death and no transplants. There were multiple subsequent pregnancies in both the PPCM and control cohorts, but the women with PPCM were more likely to have

unplanned subsequent pregnancies and more likely to end their pregnancies in terminations. All but one of the women with PPCM had recovered cardiac function prior to subsequent pregnancy and while there was 12.6% relapse rate, all of the women recovered full cardiac function post relapse.

The second aim of this dissertation was to test the hypothesis that exposure to elevated levels of $PM_{2.5}$ during pregnancy increases the risk of developing PPCM. We chose to create a cohort from the REP as it presents a unique opportunity to study relationships between environmental exposure and disease outcomes at a population level with increased generalizability compared to single or multi -center studies and to examine the effect of $PM_{2.5}$ exposure on the development of PPCM. However, due to limitations in air monitoring availability in rural areas, this hypothesis was not able to be tested with the planned study design. Instead, in Chapter 7, we present a manuscript of a case study of problems with current monitoring tools and how this hypothesis could be addressed if more complete data were available. We then provide policy recommendations to address the issues that were identified.

We initially attempted to measure $PM_{2.5}$ exposure using data from the US EPA AQS Monitoring Network by matching each study participant to the nearest $PM_{2.5}$ monitor that was active at the time of interest for each person (diagnosis date for cases and delivery date of index pregnancy for controls) using ArcGIS Pro. During this part of the study the following issues that prevented completion of the aim using monitoring data were identified: 1) 24/144 women did not have any monitoring data available as their dates of interest occurred before the first monitoring began in the study area, 2) the distance to nearest active monitor at time of interest for each woman varied significantly from 0.3 to

405.1 km with a median distance of 10.0 km, 3) due to the large distance between some residential addresses and monitoring locations the geographical locations would not be similar potentially leading to differential misclassification of exposure as controls lived further from monitors then cases, and 4) due to the matching design of the study the 24 women missing monitoring data would result in 19 case/control sets (57 women total) being dropped from the study significantly reducing the sample and possibly introducing bias. These four issues prevented us from being able to complete an analysis using EPA monitoring data for the exposure measure.

As a next step we identified two alternate methods to evaluate Aim 2 using two commonly used surrogate measures of air pollution/ $PM_{2.5}$ as exposure measures: distance to major roadway and traffic density. The first method used was distance to major roadway, which has been used in many published research studies.[2-13] When obtaining data for this option from the MN and WI Departments of Transportation we discovered that only recent years were available in a format that could be used in ArcGIS Pro and the other dates were only available as PDFs (which were not accessible due to COVID restrictions). To complete the case study, we choose to use data from 2019 which is the most recent year of ArcGIS Pro compatible data available accepting that there would potentially be non-differential misclassification bias due to changes in roads over time. We were able to use the data from 2019 to demonstrate how this type of analysis could be used if more complete data were available. However, while the initial analysis using distance to primary roadway did not show any significant difference in distance to major roadway between cases and controls, we felt that it was difficult to draw any conclusions from these data as only 3-25% of the study population lived within any of the buffered distances examined. To

address this limitation, we completed a second analysis with major roadway defined as either primary or secondary roadways, which also did not find any significant difference in distance to major roadway between cases and controls.

The second surrogate measure used to estimate exposure to $PM_{2.5}$ was annual average daily traffic (AADT) which is also commonly used in previously published studies.[2,3,7,14-21] We attempted to identify the road with the highest AADT within specific buffered distances of each residential address treating AADT both as a continuous and a categorical variable. When considering AADT as a continuous variable the results suggested that controls may live closer to higher traffic density roads, but only using a 1000m buffer; the categorical data found no significant difference in highest traffic density level between cases and controls. These data also had a number of limitations that made it difficult to draw conclusions including: 1)we could not obtain data from every year of interest for the study (again they were only available as PDFs) and had to use data from just one year leading to potential non-differential misclassification, 2) traffic counts were only conducted on each road segment once every 3 or 6 years depending on the location so that data were not available for matching the date of interest in this study, 3) within the predominantly rural study area there were no roads with AADT >125,000 which is the cut-off point used by the U.S. DOT to define major roadway, 4) when treating AADT as a continuous variable a large number of study participants had no roads with measured data within the smaller buffer sizes, and 5) when treating AADT as a categorical variable most of the higher AADT volume group categories (which are generally considered as significant exposure levels) have no, or very low, values in this predominantly rural area. An additional limitation of both surrogate measures (distance to major roadway and traffic

density) highlighted by our results, was that in rural areas, like the study area, traffic was often not the main source of $PM_{2.5}$ air pollution limiting the appropriateness of using these surrogates to measure $PM_{2.5}$ air pollution exposure in this study population.

The manuscript which is going to be submitted to the Environmental Law Reporter in Chapter 7 also addressed Aim 3 of the dissertation, which discussed the public health implications and potential policy opportunities that arise from the results of Aim 2. Based on the results of our case study traffic-based surrogates for $PM_{2.5}$ do not appear to be good measures of exposure in this rural population and $PM_{2.5}$ air monitoring would be the most accurate exposure metric. However, the current level of EPA monitoring in rural areas is not sufficient to assess relationships between $PM_{2.5}$ exposure and potential resulting health effects such as PPCM. This assessment gap also makes it difficult to determine whether $PM_{2.5}$ levels required by the Clean Air Act to protect human health are within an adequate margin of safety. To address these concerns we made the following policy recommendations:

1) Design monitoring with research in mind to improve the quality and accessibility of data to further research and not just to measure attainment which would include increasing monitoring locations while also keeping all previous monitors active continuously,
2) Increase the focus of monitoring and remediation not only for urban areas but also for non-urban areas where populations have geographical and economic differences that may lead to altered susceptibility to the adverse health effects of $PM_{2.5}$ and other air pollution which need to be studied,

3) Add pregnant women to the list of EPA designated "at-risk" populations as current research in the field supports this and doing so could increase protection for this very large group of particularly vulnerable women,
4) Increase funding available for monitoring, data acquisition and analysis, providing funding to state and local governments tasked with designing and implementing the monitoring, and fund research that uses these monitoring tools to assess the impact of pollution on human health.

Each of these 4 policy recommendations would help strengthen the human health protection from $PM_{2.5}$ exposure required by the CAA. The most recent Integrated Science Assessment for PM from the US EPA concludes that there is a casual relationship between exposure to $PM_{2.5}$ and specific cardiovascular health effects, and for the first time that exposure to $PM_{2.5}$ during pregnancy may affect maternal health,[22] but more data are needed to draw a conclusion particularly related to pregnant women. However, as the case study in this dissertation shows, currently available monitoring tools are hindering research to generate the additional data needed by the US EPA to draw a conclusion about the effects of $PM_{2.5}$ exposure on maternal health during pregnancy. The omission of endpoints like PPCM from the US EPA's analysis leaves pregnant women, a large population with potentially increased susceptibility, unprotected. Increased funding to develop and implement a monitoring system based on scientific and not just compliance measurement needs would allow the US EPA to increase protection of human health from air pollution including $PM_{2.5}$ exposure to pregnant women, and all other populations. Without these changes the US EPA may fail to meet its duty to protect human health with an adequate margin of safety as required by the Clean Air Act.

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Appendixes

Appendix 1: Published Manuscript 1

Peripartum Cardiomyopathy

Erika J. Douglass, MPH[a,b], Lori A. Blauwet, MD[c,*]

KEYWORDS

• Peripartum cardiomyopathy • PPCM • Postpartum cardiomyopathy • Pregnancy • Heart failure

KEY POINTS

- Diagnosing peripartum cardiomyopathy (PPCM) requires a high degree of suspicion, because presenting signs and symptoms tend to mimic those of normal pregnancy and the early postpartum period.
- Guideline-directed medical therapy for heart failure, with special considerations for use during pregnancy and lactation, is recommended, although efficacy and optimal duration of therapy have not been established.
- Outcomes of both mother and child are generally good, although a subset of women experience chronic heart failure, transplant, and/or cardiac death.
- Subsequent pregnancy is not contraindicated in all women with history of PPCM, because risk of cardiac complications associated with future pregnancy varies according to degree of left ventricular recovery.

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a form of heart failure with no known cause that occurs toward the end of pregnancy or in the months following pregnancy and is marked by left ventricular (LV) systolic dysfunction. Outcomes vary, because most women experience complete LV recovery, but a significant minority experience persistent cardiac dysfunction, transplant, or death.

CASE DEFINITION

The National Heart, Lung, and Blood Institute (NHLBI) and the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) Working Group (WG) on PPCM have both published definitions for PPCM[1,2] (Box 1). These 2 definitions differ in terms of timing of diagnosis and the cutoff for LV ejection fraction (LVEF). Further investigation is needed to determine potential differences between women diagnosed with PPCM using the NHLBI criteria and (1) women who present with previously undiagnosed cardiomyopathy before 1 month before delivery or greater than 5 months postdelivery, and (2) women who present with an initial LVEF greater than 45%, to determine whether or not pathophysiology and outcomes are similar. Having a clear and accurate definition of PPCM is crucial for determining optimal management strategies and prognosis and facilitating collaborative research.

EPIDEMIOLOGY

Estimates of PPCM incidence vary widely around the world, with many of the estimates coming from retrospective single-center cohort studies. Fig. 1 presents selected incidence estimates from several countries. The highest reported rates occur in Nigeria, with 995 cases per

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Box 1
Current peripartum cardiomyopathy definitions.

NHLBI[1]

- Development of cardiac failure in the last month of pregnancy or within 5 months of delivery
- Absence of an identifiable cause for the cardiac failure
- Absence of recognizable heart disease before the last month of pregnancy
- LV systolic dysfunction identified by classic echocardiographic criteria, such as ejection fraction less than 45% or fractional shortening less than 30%, or both

European Society of Cardiology[2]

- Heart failure secondary to LV systolic dysfunction with an LV ejection fraction less than 45%
- Occurrence toward the end of pregnancy or in the months following delivery (mostly in the months following delivery)
- No other identifiable cause of heart failure

(*Data from* Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. Jama. 2000;283(9):1183-1188 and Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. European journal of heart failure. 2010;12(8):767-778).

100,000 deliveries, and Togo, with 781 cases per 100,000 deliveries.[3,4] In the United States, nationwide estimates vary from 18 to 103 per 100,000 live births or deliveries.[5–9] Risk factors associated with increased risk of developing PPCM include black African descent, hypertensive diseases of pregnancy (HDPs), multifetal pregnancies, and advanced maternal age.[6,7,10–13]

PATHOPHYSIOLOGY, GENETICS, AND RISK FACTORS

The cause of PPCM is not fully understood but is most likely multifactorial. Current research suggests that hormones of late pregnancy cause a vasculotoxic environment that, in susceptible women, leads to the development of PPCM.[14,15] High levels of prolactin are secreted from the pituitary gland and can be cleaved into the vasculotoxic, proinflammatory, and proapoptotic 16-kDa form.[16] At the same time, antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) is secreted from the placenta, inhibiting vascular endothelial growth factor and placental growth factor. Both the 16-kDa form of prolactin and sFlt-1 have been shown to cause PPCM in mouse models.[17,18] sFlt-1 levels are significantly increased in women with PPCM, and higher levels at diagnosis are associated with worse outcomes.[19] Women with preeclampsia also have significantly increased sFlt-1 levels, which may at least partially explain why HDP increases risk for PPCM.[20]

A small percentage of women with PPCM have a family history of dilated cardiomyopathy (DCM). Family clustering has also been observed.[21–26] Studies have also shown that a subset of women with PPCM have genetic mutations linked to DCM, predominantly in the TTN gene, which encodes the titin protein, which is critical to cardiac muscle structure.[27–29] The Investigations of Pregnancy Associated Cardiomyopathy (IPAC) study found that 1 TTN mutation genotype was associated with lower LVEF at 6 and 12 months, especially in black women, which may help explain why black women have worse outcomes compared with white women.[30] High frequencies of mutations in the TTN gene have also been found in women with preeclampsia, which may help to explain the increased risk of PPCM in women diagnosed with HDP.[31] However, only 15% to 20% of women with PPCM have TTN mutations, and greater than 90% of individuals in the general population that have TTN mutations never develop any form of cardiomyopathy,[27–29,32] so the significance of TTN mutations in women with PPCM remains unclear. Other factors that may increase susceptibility for PPCM include oxidative stress, inflammation, viral infection, and antiangiogenic molecules.[33]

DIAGNOSIS

Because the exact cause remains unknown and no single test currently exists to confirm the diagnosis, PPCM remains a diagnosis of exclusion. Women generally present with symptoms that are common to pregnancy (orthopnea, dyspnea on exertion, fatigue, edema, paroxysmal nocturnal exertion, and chest tightness), so the diagnosis of PPCM may be delayed or missed altogether. Late diagnosis has been linked to worse outcomes, including persistent cardiac dysfunction and increased mortality.[13,34–40]

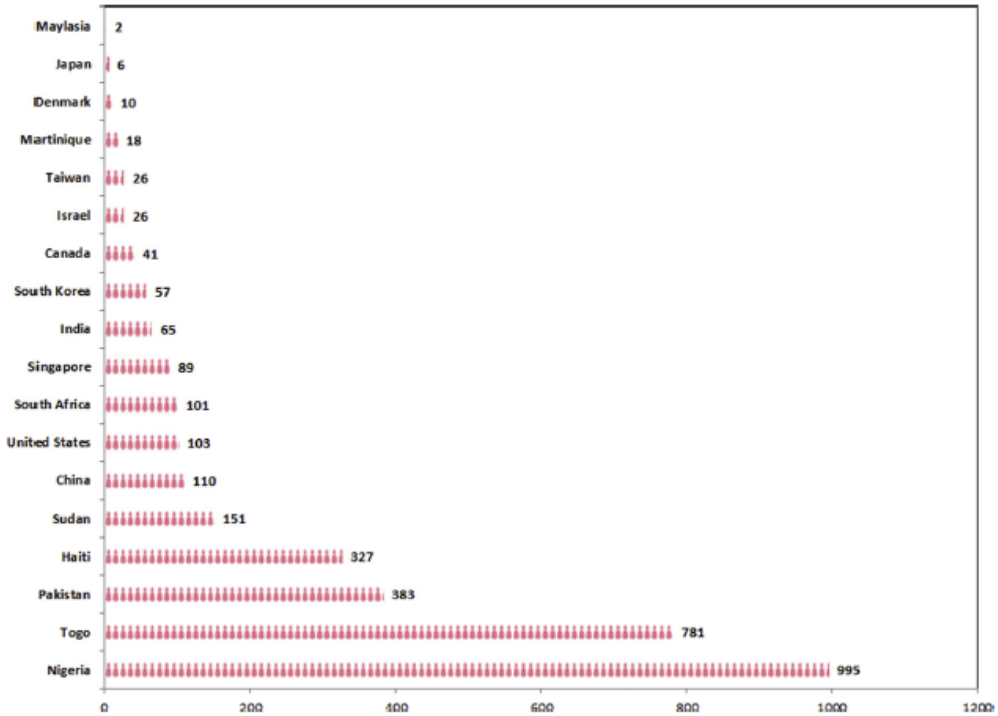

Fig. 1. Incidence of peripartum cardiomyopathy (per 100,000 live births or deliveries.) Measurements using live births: Haiti,[127] United States,[9] Singapore,[77] India,[128] Canada,[119] Martinique,[129] Japan,[130] Malaysia.[131] Measurements using deliveries: Nigeria,[3] Togo,[4] Pakistan,[132] Sudan,[133] China,[134] South Africa,[135] South Korea,[136] Israel,[118] Taiwan,[39] Denmark.[64] *Data from* Refs.[3,4,9,39,64,77,118,119,127–136]

Diagnostic Tests

Echocardiogram, electrocardiogram (ECG), chest radiograph, cardiac MRI, and laboratory testing may all be useful in the diagnosis of PPCM. Echocardiography is the most important imaging modality, because it is readily available in many health care centers and can easily and comprehensively assess cardiac structure and function. By the NHLBI definition, LVEF must be less than 45%.[1] The left ventricle is usually, but not always, dilated.[33–35,41] Assessment of right ventricular (RV) function is essential, because 3 recent articles have reported that many women with PPCM also have RV dysfunction and that these women are at higher risk for adverse outcomes.[42–44] Additional echocardiographic findings may include RV dilatation, mitral and/or tricuspid valve regurgitation, atrial enlargement, increased pulmonary pressures, and intracardiac thrombus.[33–35,41] Cardiac MRI may be useful for the evaluation of biventricular structure and function or when echocardiography is nondiagnostic, but gadolinium is not recommended for use during pregnancy.[43,45,46] Suggested diagnostic testing is outlined in Table 1.

BIOMARKERS

Many biomarker levels have been shown to be abnormal in women with PPCM and may thus be useful in diagnosing PPCM (Table 2). Markers of cardiac function such as N-terminal prohormone of brain natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), and cardiac troponin are likely the most clinically useful. No biomarkers can be used in isolation to confirm PPCM, because none are specific to this disease.

TREATMENT

Initial Management

Initial management strategies vary depending on pregnancy status (Table 3). A multidisciplinary team approach to management is recommended,

Table 1
Suggested evaluation for women with peripartum cardiomyopathy

Time Period[a]	History and Clinical Examination	Laboratory Tests[b]	Urinalysis[c]	Chest Radiograph	Chest CTA[d]	ECG	ECHO	Cardiac MRI[e]
Diagnosis	♥♥♥♥	♥♥♥♥	♥♥	♥♥♥♥	♥♥	♥♥♥♥	♥♥♥♥	♥
3 mo	♥♥♥♥	♥♥♥♥				♥♥♥♥		
6 mo	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
12 mo	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
18 mo	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
24 mo	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
>24 mo[f]	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	

♥♥♥♥, highly recommended.
♥♥, recommended in certain circumstances.
♥, consider in certain circumstances.

Abbreviations: CTA, computed tomography angiography; ECG, electrocardiogram; ECHO, echocardiogram.

[a] Timing of follow-up may vary according to presentation and clinical course.

[b] Suggested laboratory tests include complete blood count, basic metabolic panel, and brain natriuretic peptide (BNP) or N-terminal prohormone of BNP (NT-proBNP) at all times points plus aspartate aminotransferase, alanine aminotransferase, cardiac troponin, and thyroid-stimulating hormone at baseline and during follow-up, if indicated.

[c] Urinalysis is especially important for women presenting with increased blood pressure during pregnancy or the first 6 weeks postpartum to assess for preeclampsia.

[d] Consider chest CTA to assess for pulmonary embolism in patients presenting during pregnancy or the first 6 weeks postpartum.

[e] Consider cardiac MRI if patient presents during the postpartum period and echocardiography results are inconclusive.

[f] Annual follow-up should occur indefinitely.

Table 2
Biomarkers in peripartum cardiomyopathy

Biomarkers of Cardiac Function		
NT-ProBNP	May be increased[29,138,154]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
BNP	May be increased[104]	Higher levels at diagnosis are associated with persistent LV dysfunction[104,138] Higher levels at 6 mo are associated with persistent LV dysfunction[104] Higher levels at 6 mo may predict mortality[89,138] Increased levels at 3 and 6 mo may predict persistent dysfunction[69] Lower levels at 3 and 6 mo are associated with faster recovery[69]
Cardiac troponin	May be increased[154]	Higher levels at diagnosis are associated with persistent LV dysfunction[156]
Biomarkers of Inflammation		
C-reactive protein	May be increased[95,138,154,157]	Higher levels at baseline may predict mortality[157] Higher levels at baseline are correlated with worse disease[95] Increased levels at 3 and 6 mo may predict persistent dysfunction[69]
IL-6	May be increased[138,157]	Higher levels at baseline may predict mortality[157]
Tumor necrosis factor alpha	May be increased[95,138,157]	Higher levels at baseline may predict mortality[157]
IL-1β	May be increased[138]	—
Interferon gamma	May be increased[138]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
Pregnancy and Nursing Hormones		
Relaxin-2	May be decreased[158,159]	Higher levels at diagnosis are associated with recovery at 2 mo[19]
Prolactin	May be increased[138]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
Vasculotoxic Cause–related Biomarkers		
Oxidized low-density lipoprotein	May be increased[16,138]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
Fas/apoptosis antigen 1	May be increased[95,138]	Higher levels at baseline may predict mortality[95]

sFlt-1	May be increased[18]	Higher levels at diagnosis are associated with more severe disease and major adverse events[19,60]
Asymmetric dimethyl arginine	May be increased[29]	—
PlGF	May be increased[159]	—
sFlt1/PlGF ratio	May be low[159]	—
Plasminogen activator inhibitor-1	May be increased[160]	—
MicroRNAs		
miR-146a	May be increased[29,161]	—
miR-1991	May be increased[162]	—
Biomarkers of Fibrosis and Remodeling		
Galectin-3	May be increased[102]	High baseline levels are associated with poor outcomes[102]
Soluble ST2	May be increased[102]	High baseline levels are associated with poor outcomes[102]
Cleaved osteopontin	May be increased[102]	High baseline levels are associated with poor outcomes[102]
Matrix-metallo-proteinase-2	May be increased[138]	—

Abbreviations: IL, interleukin; PlGF, placental growth factor.
(*Data from* Refs[16,18,19,29,60,89,95,96,102,104,138,154,156–160,162])

particularly if the woman is pregnant or in the early postpartum period.

Medical Therapy

Women diagnosed with PPCM should be treated with guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF), bearing in mind the safety of specific medications during pregnancy and breastfeeding. Recommended medications may include β-blockers, angiotensin-converting enzyme inhibitors (ACE-Is)/angiotensin receptor II blocker (ARBs), angiotensin receptor neprilysin inhibitor (ARNIs), hydralazine/nitrates, mineralocorticoid receptor antagonists (MRAs), and diuretics. Anticoagulation should be initiated if LV thrombus is present and may be considered in women with LVEF less than 35%.

Whether or not initiating GDMT for HFrEF is necessary in all women with PPCM remains unclear, because some women recover LV function quickly and completely while taking only minimal to low doses of heart failure medications. Note that there has never been a randomized clinical trial testing the efficacy and safety of any heart failure medications in women with PPCM. Information regarding specific medications and their compatibility with pregnancy and breast feeding is reviewed Karen L. Florio and colleagues' article, "Cardiovascular Medications in Pregnancy: A Primer," in this issue.

Bromocriptine

Bromocriptine, which inhibits the nursing hormone prolactin, has been proposed as a novel treatment of PPCM in response to the hypothesis that the development of PPCM is driven by the antiangiogenic and proapoptotic 16-kDa cleaved form of prolactin. A small proof-of-concept study with 20 women in South Africa found that the addition of bromocriptine led to greater recovery of LVEF and lower mortality at 6 months.[47] A second study in Burkina Faso showed that treatment with bromocriptine was associated with increased LVEF at 2 weeks and at 3, 6, and 12 months, as well as decreased mortality.[48] However, both studies had unusually high rates of mortality in the control groups, limiting the ability to generalize the results. A multicenter randomized study with no control group conducted in Germany compared 2 dosing regimens (1 week vs 8 weeks) of bromocriptine in addition to GDMT for heart failure.[49] Both study groups had similar outcomes, with no women undergoing heart transplant and

Table 3
Initial management of peripartum cardiomyopathy

	Hemodynamically Stable	Hemodynamically Unstable	Hemodynamically Stable	Hemodynamically Unstable
Consult Cardio-obstetrics specialist				
Consult High-risk obstetrics (maternal fetal medicine) specialist			—	—
Form multidisciplinary team to prepare delivery plan			—	—
Consider early delivery	—		—	—
Arrange for fetal monitoring during labor and delivery			—	—
Initiate selected oral heart failure medications (eg, diuretics, nitrates, hydralazine, digoxin)			—	—
Initiate oral GDMT for HFrEF (eg, β-blocker, ACE-I, ARB, ARNI, MRA, diuretics [modify if lactating])	—	—		(after stabilized)
Consider using inotropes	—		—	
Initiate anticoagulation if LV thrombus				

(*continued on next page*)

Table 3
(continued)

	Hemodynamically Stable	Hemodynamically Unstable	Hemodynamically Stable	Hemodynamically Unstable
Consider anticoagulation if LVEF <35%	—	—		
Plan for vaginal delivery		—	—	—
Plan for probable cesarean delivery	—		—	—
Provide supplemental oxygen and/or noninvasive ventilation, if hypoxic		—		—
Intubate and ventilate if hypoxic despite noninvasive ventilation	—		—	
Consider advanced heart failure therapies[a] if failure to respond to medical therapy (and delivery)	—		—	
Discuss lactation preferences	—	—		—
Discuss contraception	—	—		

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

[a] Mechanical circulatory support/ventricular assist device/cardiac transplant.

no mortality in either group. The lack of a control group limits the applicability of these results in current clinical practice.

In addition to the lack of rigorous clinical research showing the efficacy of bromocriptine for treatment of acute PPCM, concern regarding potential serious adverse effects has limited routine administration of bromocriptine in clinical practice. Treatment with bromocriptine has been associated with stroke, myocardial infarction, and seizures and, as a result, it is no longer marketed for elective lactation suppression in the United States.[34] If bromocriptine is used, anticoagulation should be administered for the duration of therapy because women are already in a hypercoagulable state during the peripartum period and bromocriptine may further increase hypercoagulability.

Of particular importance, women treated with bromocriptine cannot breastfeed their infants. The World Health Organization recommends exclusive breastfeeding for 6 months and continued breastfeeding for at least 1 to 2 years because of the importance of breastfeeding to the health of both mother and infant. Not breastfeeding is associated with increased risk of diabetes, ovarian and breast cancer, and postpartum depression for mothers, and higher rates of mortality, infections, eczema, asthma, childhood obesity, type 2 diabetes, leukemia, and lower intelligence in children.[50,51] Results of the IPAC study and 2 retrospective cohort studies suggest that breastfeeding has no detrimental effect on outcomes for women with PPCM.[52–54]

The most recent statement on PPCM by the HFA ESC WG PPCM lists treatment with bromocriptine as a class IIb recommendation.[41] In contrast, the American Heart Association (AHA) and the Canadian Cardiovascular Society (CCS) both recommend that bromocriptine should not routinely be used in the treatment of PPCM until more rigorous data that support the safety and effectiveness of its use are available.[35,55]

Chronic Management

Most experts agree that GDMT for HFrEF should be continued indefinitely in women with PPCM who have persistent cardiac dysfunction. The optimal duration of treatment of women who recover normal LV function is unknown. A 2016 AHA scientific statement on the diagnosis and treatment of dilated cardiomyopathies recommended indefinite continuation of treatment in women with PPCM, including those with recovered cardiac function, as well as yearly clinical follow-up and assessment of LV function even after recovery.[35] More recent articles suggest that treatment duration should be considered on a case-by-case basis, with changes to or discontinuation of any cardiac medications to be completed slowly using a stepwise approach with frequent clinical and echocardiographic monitoring and follow-up.[34,41] The HFA ESC WG PPCM has published recommendations for women diagnosed with PPCM who have recovered LV function (LVEF>55%) and are New York Heart Association (NYHA) functional class I as follows: continuation of all cardiac drugs for at least 12 to 24 months after full recovery and then discontinue them in a stepwise fashion (first MRA, second ACE-I/ARB/ARNI, and then β-blocker) with frequent monitoring of symptoms and LV function.[41] Thus, although both the AHA and HFA ESC WG PPCM guidelines agree that diuretics can be tapered and discontinued if there are no signs of fluid overload, there is no consensus regarding duration of other cardiac medications in individual women.

Several studies and case reports have shown that some women with PPCM who have recovered LV function can safely be tapered off medical therapy.[36,56–58] In 1 study, 5 women were tapered off all cardiac medications and none experienced deterioration of LV function over an average follow-up duration of 29 months (range, 5–63 months.)[58] Another report found that 2 women who had fully recovered LV function had deterioration of LVEF after discontinuation of all cardiac medications, with deterioration occurring at 24 and 34 months after diagnosis.[57] Two more recent studies found that women with LV recovery may have high rates of LV diastolic dysfunction and reduced exercise capacity[59] as well as ongoing angiogenic imbalance and residual myocardial injury,[60] suggesting that women who recover may benefit from long-term GDMT for HFrEF.

Long-term cardiology follow-up of women with history of PPCM who have recovered LV function is recommended regardless of whether or not LV recovery occurs and/or cardiac medications are discontinued (see Table 1).

Advanced Heart Failure Therapies

Women with PPCM who have severe myocardial disease may benefit from a wearable or implantable cardiac defibrillator, left ventricular assist device (LVAD), mechanical circulatory support (MCS), and/or transplant. Multiple factors affect the rates of each of these types of advanced heart failure therapy, including time to diagnosis, race, and availability. Rates of use of each of these advanced therapies in women with PPCM are difficult to discern, because studies often do not list

these therapies separately and have combined these outcomes differently for reporting. A nationwide study conducted in the United States reported that, between 2004 and 2011, 1.5% of patients with PPCM required MCS and 0.5% of patients underwent transplant.[9] Study specific rates in the United States vary between 0% and 7.8% for defibrillator implantation, 0% to 17.2% for MCS (intra-aortic balloon pump, LVAD, and extracorporeal membrane oxygenation), and 0% to 8.8% for transplant.[11,36,40,61–63] Rates in other countries vary widely, often depending on the availability of these advanced treatment options.[39,56,63–71]

OUTCOMES

Mortality

Women with PPCM tend to have lower mortalities than women with other forms of DCM.[72,73] Reported mortalities related to PPCM vary widely both within and between countries and within similar follow-up durations (Table 4). A recent systematic review and meta-analysis by Kerpen and colleagues[74] found the overall PPCM mortality to be 9%, with higher rates in developing countries (14%) compared with more advanced countries (4%). Fig. 2, which includes 9 countries in addition to the 13 included in the meta-analysis by Kerpen and colleagues,[74] shows a similar trend of higher mortalities in developing countries. The higher PPCM mortalities in developing countries are most likely related to the impact of social determinants of health, including reduced access to care in general and access to advanced heart failure therapies in particular.

Mortalities in Taiwan and the United States seem to be exceptions among advanced countries, whereas rates in The Philippines, China, and Singapore do not follow the trend among developing countries. Small sample sizes[75–77] and differences in methodologies and populations, particularly among the US reports,[7–9,11–13,36,38,40,43,58,61,62,72,73,78–87] may account for these variations.

Left Ventricular Recovery

Similar to mortality, women with PPCM tend to have higher rates of LV recovery than women with other forms of DCM.[72,73] Recovery rates differ between countries, from 28% in Haiti[88] to 43% in Israel,[71] 48% in Turkey,[89] 47% in Germany,[29] 55% in South Africa,[90] 63% in Japan,[67] and 67% in Denmark.[64] There is a wide variation in recovery rates within the United States as well, with reported rates ranging between 23% and 72%.[38,40,58,61,78,84,86,91,92] Lack of consensus in the definition of LV recovery (LVEF>45% vs 50%, vs 55%, or any recovery vs a specific percentage increase in LVEF) and follow-up time (6 months vs 12 months vs longer) contributes to the large range in reported LV recovery rates among studies across the globe.

Timing of LV recovery varies, with some women recovering in days to weeks, whereas other women require months to years. An article from Israel reported that 22% of women with PPCM achieved full recovery (LVEF $\geq$ 50%) within 2 weeks, a further 30.1% recovered by 1 year, and an additional 13.8% recovered between 1 and 10 years.[71] The mean time to recovery in a study of 44 women in the United States was 54 months.[86] In Haiti, reported recovery time ranged from 3 to 38 months and in Turkey from 3 to 42 months (mean, 19.3 months).[69,93] One study completed in the United States found that 83% of women who recovered did so after more than 6 months of follow-up, whereas another study reported that 25% of women who recovered did so between 2 and 8 years after diagnosis.[84,94] The wide range of time to LV recovery underlines the importance of long-term cardiac follow-up of women with PPCM.

Predictors of Outcome

Many factors have been evaluated for their potential to predict outcomes in PPCM, particularly the risks for persistent myocardial dysfunction and death. The most reliable predictor has been found to be LVEF at diagnosis, with studies consistently reporting that women with lower LVEF (particularly <30%) at diagnosis are less likely to recover and more likely to experience adverse outcomes, including death.[29,36,38,40,57,58,61,78,80,83,86,91,92,95,96] Studies have also reported that the degree of LV dilatation may be a useful predictor, with larger LV end-diastolic diameter (LVEDD) being associated with lack of LV recovery and death.[29,40,57,58,78,92,96,97] LV dilatation and LVEF were combined as predictors in the IPAC study, which found that 91% of women with LVEF greater than or equal to 30% and LVEDD less than 60 mm recovered.[40] The IPAC study also reported that LV global longitudinal strain at presentation was associated with clinical outcomes and may be useful for risk stratification in addition to LVEF.[98] RV fractional area change at diagnosis was shown to be a strong predictor of outcomes in the IPAC study,[44] whereas another study in the United States found that moderate to severe RV dysfunction was associated with more severe disease and higher risk of adverse outcomes.[43] T-wave abnormalities on

Table 4
Studies with greater than or equal to 50 subjects reporting mortality among women with peripartum cardiomyopathy

First Author	Follow-up Duration	Actual, Mean, Median	Country	Data Source	Study Years	Sample (n)	Mortality (%)
In Hospital							
Kolte et al,[9] 2014	NA	NA	United States	Nationwide Inpatient Sample database	2004–2011	34,219	0.0
Krisnamoorthy et al,[80] 2016	NA	NA	United States	Nationwide Inpatient Sample database	2009–2010	4871	0.0
Lee et al,[136] 2018	NA	NA	South Korea	Korean National Health Insurance Database	2010–2012	795	1.0
Masoomi et al,[8] 2018	NA	NA	United States	Nationwide Readmissions Database	2013	568	1.2
Kao et al,[11] 2013	NA	NA	United States	Inpatient administrative databases for 6 states	2003–2007	535	1.3
Mielniczuk et al,[7] 2006	NA	NA	United States	National Hospital Discharge Survey	1990–2002	16,269	1.9
1–6 mo							
Azibani et al,[102] 2020	6 mo	Actual	Germany	1 hospital	Missing	73	0.0
Dhesi et al,[119] 2017	6 mo	Actual	Canada	Multiple databases linked together covering all of Alberta	2005–2014	194	1.5

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Table 4
(*continued*)

First Author	Follow-up Duration	Actual, Mean, Median	Country	Data Source	Study Years	Sample (n)	Mortality (%)
Huang et al,[154] 2012	21.6 d	Mean	China	1 hospital	2007–2009	52	1.9
Tibazarwa et al,[90] 2012	6 mo	Actual	South Africa	1 hospital	2003–2008	78	3.8
Libhaber et al,[97] 2015	6 mo	Actual	South Africa	2 hospitals	Missing	206	12.6
Blauwet et al,[106] 2013	6 mo	Actual	South Africa	1 hospital	Missing	162	13.0
Azibani et al,[102] 2020	6 mo	Actual	South Africa	1 hospital	Missing	56	14.3
Sliwa 2006 et al,[95] 2006	6 mo	Actual	South Africa	1 hospital	Missing	100	15.0
7–12 mo							
Kamiya et al,[67] 2011	9.6 mo	Mean	Japan	Nationwide survey of medical locations	2007–2008	102	3.9
Isezuo et al,[3] 2007	9.7 mo	Mean	Nigeria	1 hospital	2003–2005	65	12.3
1–2 y							
Phan et al,[79] 2020	1 y	Actual	United States	Southern California Kaiser Healthcare System	2003–2014	333	0.3
Erbsoll et al,[64] 2017	10–14 mo	Actual	Denmark	Danish National Patient Register, Medical Birth Registry, Causes of Death Registry	2005–2014	61	1.6

McNamara et al,[40] 2015	1 y	Actual	United States	IPAC: nationwide cohort of 100 women	2009–2012	100	4.0
Goland et al,[12] 2013	1.6 y	Mean	United States	2 hospitals	1993–2000	156	7.1
Wu et al,[39] 2017	1 y	Actual	Taiwan	National health insurance database	1997–2011	742	7.3
Elkayam et al,[38] 2015	1.9 y	Mean	United States	Survey mailed to doctors nationwide and data from 1 hospital	Missing	100	9.0
Sliwa et al,[140] 2011	2 y	Actual	South Africa	1 hospital	Missing	60	36.7
>2 y							
Amos et al,[58] 2006	3.6 y	Mean	United States	1 hospital	1990–2003	55	0.0
Habli et al,[78] 2018	3.4 y	Mean	United States	2 hospitals	2000–2006	70	0.0
Li et al,[104] 2016	3.6 y	Mean	China	1 hospital	2004–2011	71	0.0
Moulig et al,[152] 2019	5 y	Actual	Germany	1 hospital	2006–2013	66	1.5
Gunderson et al,[13] 2011	3 y	Actual	United States	Northern California Kaiser delivery hospitals	1995–2004	110	1.8
Peters et al,[43] 2018	3.6 y	Median	United States	1 hospital	1992–2016	53	1.9
Brar et al,[81] 2007	4.7 y	Mean	United States	Southern California Kaiser Healthcare System	1996–2005	60	3.3
Ekizler et al,[163] 2019	5.6 y	Median	Turkey	1 hospital	2009–2017	82	7.3

(*continued on next page*)

Table 4
(*continued*)

First Author	Follow-up Duration	Actual, Mean, Median	Country	Data Source	Study Years	Sample (n)	Mortality (%)
Pillarisetti et al,[84] 2014	2.9 y	Mean	United States	2 hospitals	1999–2012	100	11.0
Fett et al,[150] 2005	2.2 y	Mean	Haiti	1 hospital	2000–2005	98	15.3
Akil et al,[66] 2016	2.7 y	Mean	Turkey	3 hospitals	2002–2012	58	15.5
Harper et al,[62] 2012	7 y	Actual	United States	1 hospital	2002–20,030	85	16.5
Biteker et al,[69] 2020	3.4 y	Mean	Turkey	1 hospital	2005–2016	52	19.2
Mahowald et al,[61] 2019	6.3 y	Mean	United States	1 hospital	2000–2011	59	20.3
Mishra et al,[145] 2006	6.1 y	Mean	India	1 hospital	1995–2005	56	23.2

Abbreviation: NA, not available.
(*Data from* Refs.[3,7–9,11–13,38–40,43,58,61,62,64,66,69,78,79,81,84,90,95,97,102,104,106,119,136,140,145,150,152,154])

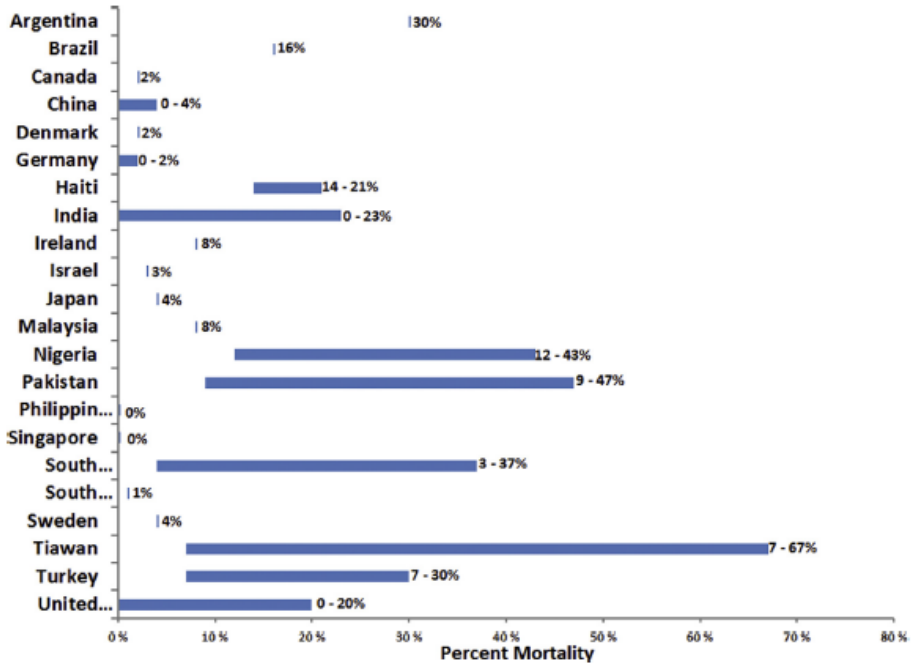

Fig. 2. Percentage mortality estimates for peripartum cardiomyopathy. Twenty-four countries are represented, 12 of which only had 1 estimate available, whereas each of the other 10 countries had between 2 and 25 estimates available. For countries with only 1 estimate available, that value is indicated. For the countries with multiple estimates available, ranges are presented showing the highest and lowest estimates for each country. *Data from* Refs.[7–9,11–13,36,38–40,42,43,47,56–58,61,62,64–70,73,75–87,95,97,99,102,106,119,131,136–155]

ECG have been suggested as a useful tool for predicting adverse outcome in PPCM, which could be advantageous in resource-poor settings in which echocardiographic evaluation may not be readily available.[90,99]

Other factors that also seem to affect outcomes include race, HDP, and body mass index (BMI). Studies in the United States show that, compared with nonblack women, black women have worse outcomes, including slower and less complete recovery of LV function and higher rates of defibrillator use, transplant, and mortality.[36,40,61,91,100–103] A recent meta-analysis found that studies with higher rates of African women tend to have higher mortalities.[74] History of HDP during index pregnancy may also be important, with multiple studies finding an association between HDP and improved rates of recovery and reduced mortality.[29,40,52,64,67,94,97,104] The IPAC study found that higher BMI is associated with less cardiac recovery at 6 and 12 months,[105] whereas a study including predominantly black African women in South Africa found that lower BMI was associated with a worse combined end point of death, LVEF less than 35%, or remaining in NYHA functional class III/IV at 6 months.[106] Women with multiple predictors of poor outcome may be at increased risk of persistent cardiac dysfunction and death, but this remains speculative because of limited data. Multiple biomarkers have been investigated for their potential usefulness in predicting which women are more likely to experience adverse outcomes, but none have been validated for clinical use (see Table 2).

SUBSEQUENT PREGNANCY

Many women with history of PPCM desire to become pregnant again. One recent study found that 74% of women diagnosed with PPCM desire to have more children and 1 in 4 women with PPCM who are sexually active were not using birth control.[107] All women with PPCM are at risk of declining LV function during subsequent pregnancy, but the risk is not necessarily prohibitive. Although some women experience worsening LV function or even death with subsequent pregnancy, others are able to complete a subsequent pregnancy without cardiac complications. Having

1 subsequent pregnancy without heart failure relapse does not ensure that a woman will not experience worsening heart function during a future subsequent pregnancy and vice versa.[83,108–110] At present, there is no clear method to identify with certainty which women will experience adverse cardiac events with subsequent pregnancies. The risk of heart failure relapse is highest in women who have persistent LV dysfunction at the onset of a subsequent pregnancy, with up to 50% having further decline in LV function during subsequent pregnancies.[111–114] Women with recovered LV function have an approximately 20% chance of heart failure relapse as defined in various studies by either experiencing heart failure symptoms and/or decrease in LVEF.[108,111–114]

The AHA, the CCS, and the HFA ESC WG PPCM stratify recommendations regarding subsequent pregnancy based on LV function, recommending that women with partial or fully recovered LV function be advised that they may consider subsequent pregnancy, whereas women with lack of LV recovery should be advised against subsequent pregnancy.[35,55,113] Despite these recommendations, studies show that only 59% to 75% of women diagnosed with PPCM report receiving counseling on the risk of subsequent pregnancy.[107,115] Importantly, qualitative studies have shown that women report feeling that the counseling provided tends to be limited, with women simply being told that they should not get pregnant again rather than engaging in an informed discussion with a health care provider.[116,117] These findings indicate that discussions regarding contraception and potential risks of subsequent pregnancy should occur with informed health care providers who can provide accurate information and are willing to participate in a shared decision-making process.

All women considering or undergoing subsequent pregnancy, regardless of cardiac function before conception, should be closely monitored by a multidisciplinary team from before conception through to several months postpartum in order to identify potential cardiac compromise as early as possible so as to optimize management and improve outcomes.[35,111,113] Recommended cardiac monitoring includes clinical evaluation, BNP or NT-proBNP, and echocardiogram either just before conception or within the first trimester, at 6 months' gestation, 9 months' gestation, before hospital discharge after delivery, and 1 month after delivery, with the timeline and type of follow-up adjusted according to the patient's clinical status.

ADDITIONAL CLINICAL CONCERNS

Infant Outcomes

The few studies of PPCM that include infant outcomes suggest that PPCM diagnosis in mothers is related to increased adverse outcomes in the infants, including higher rates of preterm and premature birth,[13,87,118,119] increased risk of being born small for gestational age,[13,118] increased rates of low birth weight,[13,87,118,119] and lower Apgar scores at both 1 and 5 minutes.[13,87,118] In women with PPCM, rates of premature birth (<37 weeks' gestation) vary between 25% and 60%[13,38,87,104,119] and are significantly increased compared with controls (25.4% vs 8.6% $P<.01$[119] and 27.9% vs 7.3%; $P<.001$[13]). Mean birthweight for infants born to mothers with PPCM ranged between 2378 and 3178 g,[38,56,64,71,76,78,84,87,118,119] and 2 studies with controls found that birth weights were significantly lower in infants born to mothers with PPCM (2697 vs 3165 g, $P<.002$[118]; and 3188 vs 3331 g, $P<.01$[119]).[13,38,56,64,71,78,84,87,118,119] Two studies that examined Apgar scores at 1 and 5 minutes found both to be significantly lower in infants born to mothers with PPCM compared with those born to mothers without PPCM.[13,118]

Premature birth, low birth weight, and lower Apgar scores are all known to be associated with greater risk of infant mortality and a variety of early and late developmental and other medical issues.[120] However, information regarding these outcomes in children of women with PPCM remains limited because infant outcomes in PPCM have only rarely been assessed in research studies.

Mental Health

Depression is a well-known risk factor for heart disease, and depression and anxiety are linked to worse outcomes in heart failure.[121,122] Women diagnosed with PPCM tend to be young mothers who were previously in the prime of their lives and now must juggle a diagnosis of heart failure while caring for a newborn, a household, and possibly other children. These stresses increase the risk for mood disorders. High levels of generalized anxiety, cardiac anxiety, and quality-of-life concerns are present in more than 50% of women with PPCM, and 56% of women with PPCM never return to their baseline emotional states after PPCM diagnosis.[115] Although only 3% to 7% of women with PPCM have a history of depression before PPCM diagnosis,[9,64,80] the rate of depression in women after diagnosis with PPCM has been reported to be 32.3%,[123] which is higher than the reported rate of 11.5% among

Box 2
Knowledge gaps in peripartum cardiomyopathy requiring further evidence-based investigation

Research questions

Diagnosis

- How can women who are susceptible to developing PPCM be identified before pregnancy?

Pathophysiology and genetics

- What is the exact pathophysiology/pathophysiologies of PPCM?
- To what extent to do genetic variations contribute to the development of PPCM and influence outcomes?

Diagnosis

- Is there a PPCM-specific biomarker, or set of biomarkers, that can be used to diagnose PPCM with a high degree of certainty?

Treatment

- Which, if any, typical heart failure medications are beneficial for treating all women with PPCM?
- How long should GDMT for HFrEF be continued in women with PPCM who have completely recovered LV function?
- Is bromocriptine safe and effective for treatment of acute PPCM?
- When is the use of wearable defibrillators indicated?
- When should an implantable cardioverter defibrillator be recommended?
- What is the most appropriate type and timing of follow-up in women who have recovered LV function versus those who have not?

Outcomes

- What are the best clinical predictors of outcome for women with PPCM that could be available in various health care resource settings?
- What are the very-long-term (ie, decades after diagnosis) outcomes for women with history of PPCM?
- Do women with history of PPCM have higher risk of developing other types of cardiac disease as they age?

Subsequent pregnancy

- What are the risks of cardiac deterioration and death with subsequent pregnancy with women with history of PPCM and those who have recovered LV function versus those who have not?
- Are there management strategies that are useful to reduce the risk of adverse outcomes in women during a subsequent pregnancy?

Infant outcomes

- What are the short-term and long-term health risks for infants born of mothers with PPCM?
- Are there strategies than can mitigate these risks?

Mental and emotional health

- Are there safe and effective strategies that can be used to decrease the burden of mental and emotional health issues affecting women with PPCM and their families?

Issues to be addressed in order for future research to adequately address knowledge gaps

- Global agreement on the definition of PPCM
- Global agreement on the definition of LV recovery
- Global agreement on the definition of relapse during subsequent pregnancy
- Funding for large, multicenter, well-designed, and well-adjudicated prospective registries and clinical trials

postpartum women in the United States.[124] Notably, there has been an association reported between depression and lower adherence to appointments for PPCM.[123] Qualitative studies suggest that an underlying issue for ongoing emotional and mental distress is lack of inclusion of the women and their partners in discussions and decisions related to the women's care and prognosis, with 35% of women in 1 study thinking that they had not been adequately counseled and another 33% thinking they were left with unaddressed questions.[115–117,123,125,126]

The HFA ESC WG PPCM and AHA both advise that each woman with PPCM be assessed and followed during subsequent pregnancy by a multidisciplinary team including cardiology, obstetrics, maternal-fetal medicine, neonatology, anesthesiology, and possibly other specialties.[35,113] Given the high incidence of mood disorders in women with history of PPCM, including mental health specialists or social workers on the multidisciplinary team to help address the long lasting emotional and psychological impact of PPCM would be beneficial, not only during subsequent pregnancy but after initial diagnosis as well.

SUMMARY

Although rare, PPCM can have a profound effect on previously healthy young women. Numerous advances have been made in understanding the cause, pathophysiology, and natural history of this disease, but many knowledge gaps remain (Box 2). Large prospective studies and randomized clinical trials are needed to address these knowledge gaps and to facilitate development of evidence-based guidelines regarding the diagnosis and management of PPCM. In addition, it is of utmost importance that management decisions regarding women with PPCM be formulated among a multidisciplinary team using a shared decision-making approach with the patients and their families in order to optimize diagnosis, treatment, and outcomes for all concerned.

CLINICS CARE POINTS

- Women diagnosed with PPCM benefit from evaluation and treatment by a multidisciplinary team including members from cardiology, maternal fetal medicine, obstetrics, social work, mental health and other specialties as indicated.
- Obtaining a complete patient and family cardiac history is important in order to establish the diagnosis of PPCM, as PPCM is a diagnosis of exclusion.
- Clinicians should have a low threshold for obtaining cardiac testing, including an ECG, echocardiogram, and B-type natriuretic peptide (BNP) or N-terminal proBNP, in pregnant/postpartum women who present with signs/symptoms suggestive of heart failure, even though the signs/symptoms may seem typical for women who are pregnant or postpartum.
- No biomarkers, including troponin T, troponin I, B-type natriuretic peptide (BNP) or N-terminal proBNP, are specific for the diagnosis or PPCM.
- Bromocriptine may be helpful for treatment of acute PPCM, particularly in postpartum women with severely depressed LVEF, but the safety and efficacy of this medication for treatment of PPCM has not yet been established.
- Clinicians must be cognizant of which of the guideline directed mediations for heart failure are safe to use during pregnancy and which are safe to use during lactation.
- Contraceptive counseling during the postpartum period and on a regular basis thereafter is imperative in order to prevent unplanned pregnancy.
- Women with history of PPCM should be counseled about the risk of subsequent pregnancy, bearing in mind that women who have recovered normal LV function are generally able to complete a subsequent pregnancy without significant complications.
- Screening women with PPCM for anxiety and depression in both in the acute and chronic care setting is essential for optimizing management of their mental and physical health.

DISCLOSURE

The authors have nothing to disclose.

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Appendix 2: Published Manuscript 2

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A Case-Control Study of Peripartum Cardiomyopathy Using the Rochester Epidemiology Project

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ABSTRACT

Background: The incidence of peripartum cardiomyopathy (PPCM) is known through referral center databases that may be affected by referral, misclassification, and other biases. We sought to determine the community-based incidence and natural history of PPCM using the Rochester Epidemiology Project.

Methods and Results: Incident cases of PPCM occurring between January 1, 1970, and December 31, 2014, were identified in Olmsted County, Minnesota. A total of 15 PPCM cases were confirmed yielding an incidence of 20.3 cases per 100,000 live births in Olmsted County, Minnesota. Clinical information, disease characteristics, and outcomes were extracted from medical records in a 27-county region of the Rochester Epidemiology Project including Olmsted County and matched in a 1:2 ratio with pregnant women without PPCM. A total of 48 women were identified with PPCM in the expanded 27-county region. There was 1 death and no transplants over a median of 7.3 years of follow-up. Six of the 23 women with subsequent pregnancies developed recurrent PPCM, all of whom recovered. Migraine and anxiety were identified as novel possible risk factors for PPCM.

Conclusions: The population-based incidence of PPCM was 20.3 cases per 100,000 live births in Olmsted County, Minnesota. Cardiovascular outcomes were generally excellent in this community cohort. (*J Cardiac Fail 2021;27:132–142*)

Key Words: Heart failure, incidence, migraine, pregnancy.

Peripartum cardiomyopathy (PPCM) is defined as the development of cardiac failure in the last month of pregnancy or within 5 months of delivery in women with no history of heart disease and no other identifiable cause for cardiac failure. PPCM is characterized by left ventricular (LV) systolic dysfunction with an LV ejection fraction (LVEF) of ≤45% and confirmed by echocardiography,[1] as well as heart failure symptoms. Women with PPCM can experience complete recovery of heart function[2,3] with early diagnosis and treatment. Timely diagnosis is challenging because the symptoms of PPCM are similar to the physiological changes that occur during normal pregnancy and postpartum.[4,5]

The incidence estimates of PPCM vary widely between countries and within the United States from 25 cases per 100,000 live births in the United States[6] to 333 per 100,000 live births in Haiti.[7] Within the United States, rates vary from 25 cases per 100,000 live births in southern California to 185 per 100,000 live births in Georgia.[5,6,8–13] The first population-level estimate of PPCM incidence in the United States used the National Hospital Discharge Survey, relying on *International Classification of Diseases* (ICD) codes to confirm the diagnosis, and reported 31 cases per 100,000 live births.[13] A population-level study of PPCM with a complete medical record review for data abstraction has not been published previously. This study provides the first population-level epidemiologic study describing the incidence and outcomes of PPCM using a comprehensive

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medical record review through the Rochester Epidemiology Project (REP) using a case-control design to examine demographic and clinical characteristics, presentation, potential risk factors, and outcomes.

Methods

Participants

This project was approved by both the Mayo Clinic and Olmsted Medical Center Institutional Review Boards and conformed to the principles set forth in the Declaration of Helsinki 1975, as revised in 2013. All patients involved in the study provided written informed consent to allow the use of their medical records for research purposes as part of the REP. Patients who had not previously consented to participate in research through the REP were excluded from the study.

Source of Data

The REP has been used to conduct population-level epidemiologic research in Olmsted County, Minnesota, as described previously.[14] Briefly, the database links the medical record of most health care providers in the county, including Mayo Clinic and Olmsted Medical Center and their affiliated hospitals as well as a few private providers who provide 90%–96% of all health care to Olmsted County residents.[14-16] Data for this study was available from 3 regions: Olmsted County (1 county), a 7-country region that included Olmsted County and 6 other surrounding counties, and a 27-county region that incorporated the 7 counties as well as other counties in southern Minnesota and western Wisconsin.[17] Olmsted County has a coverage rate of 99.9% from January 1, 1970, through December 31, 2014, and the 7-county region has a 93.8% coverage rate from January 1, 1976, through December 31, 2014. Starting January 1, 2010, the REP was expanded to include a total of 27 counties.[14–17] The 27-county region uses the same data linkage system as the REP and has an overall coverage rate of 60.9% from January 1, 2010, to December 13, 2014.[14-17] The lower coverage rate is due predominantly to not all heath care facilities within the region collaborating in the REP.[17] The REP has electronic indexes that include demographic information, diagnostic and procedure codes, health services use data, outpatient drug prescriptions, laboratory test results, imaging and procedure reports, and information about smoking, height, weight, and body mass index.[14–17] The demographic, racial, ethnic, and socioeconomic makeup of the 27 county region REP has been shown to be representative of the Minnesota/Wisconsin area and to a large segment of the US population.[17]

Study Population

Data were collected for all Olmsted County, Minnesota residents diagnosed with PPCM from January 1, 1970, through December 31, 2014. PPCM cases from the 1-county region were broadly identified from a list of 866 women 15–55 years of age living in Olmsted County, Minnesota, from 1970 to 2014 with a PPCM diagnosis code (ICD-9 674.5X, Hospital International Classification of Disease Adaptation [HICDA] 4251610, 4251310, BRK 0234 × 1) or a heart failure code (ICD-9 428.X, HIC 4270110, 4279133, BRK 23452); codes that were used for these disease classifications during this time period. The older HICDA code was used to identify PPCM cases during the years before the use of ICD-9 diagnosis codes. From the original 866 patients identified with possible PPCM, 15 cases were confirmed as PPCM. Population-level data were only available for Olmsted County, so the incidence of PPCM was based on Olmsted County data.

To increase the sample size of the study, data were also collected from January 1, 1976, through December 31, 2014, by individual record review for the 7-county and the 27-county regions. Because heart failure diagnosis codes had not yielded any additional cases of PPCM in the survey of 866 records in Olmsted County, only diagnosis codes for PPCM (ICD-9 674.5X) or cardiomyopathy (HICDA 4250310) were used for the expanded regions. From the 7-county region, we identified an additional 242 women with PPCM diagnoses, and a further 69 patients from the 27-county region with PPCM diagnoses. From these potential cases, medical record review confirmed 33 additional cases of PPCM, which combined with the 15 cases from Olmsted County, provided a total of 48 cases for the study (Fig. 1).

In total, 1177 potential cases of PPCM were individually screened from all 3 regions using a case definition for PPCM based on the criteria proposed by the National Heart, Lung and Blood Institute and the Office of Rare Diseases of the National Institutes of Health Workshop on Peripartum Cardiomyopathy[1] that included (1) the development of cardiac failure in the last month of pregnancy or within 5 months of delivery, (2) an absence of an identifiable cause for the cardiac failure, (3) an absence of recognizable heart disease before the last month of pregnancy, and (4) a LV systolic dysfunction demonstrated by classical echocardiographic criteria with an EF of ≤45% (Fig. 1).

Control patients were selected from a pool of 52,682 women 15–55 years of age who lived and gave birth within the 27-county region of the REP from January 1, 1970, through December 31, 2014. Controls were matched on a 2:1 basis by age, race, and number of babies born during the index pregnancy (index pregnancy refers to the pregnancy related to initial PPCM diagnosis for cases and the matched pregnancy in each control).

Data Collection

Data regarding demographics, medical history, index pregnancy, and outcomes for the 48 confirmed PPCM cases and the 96 selected controls were abstracted from electronic and paper

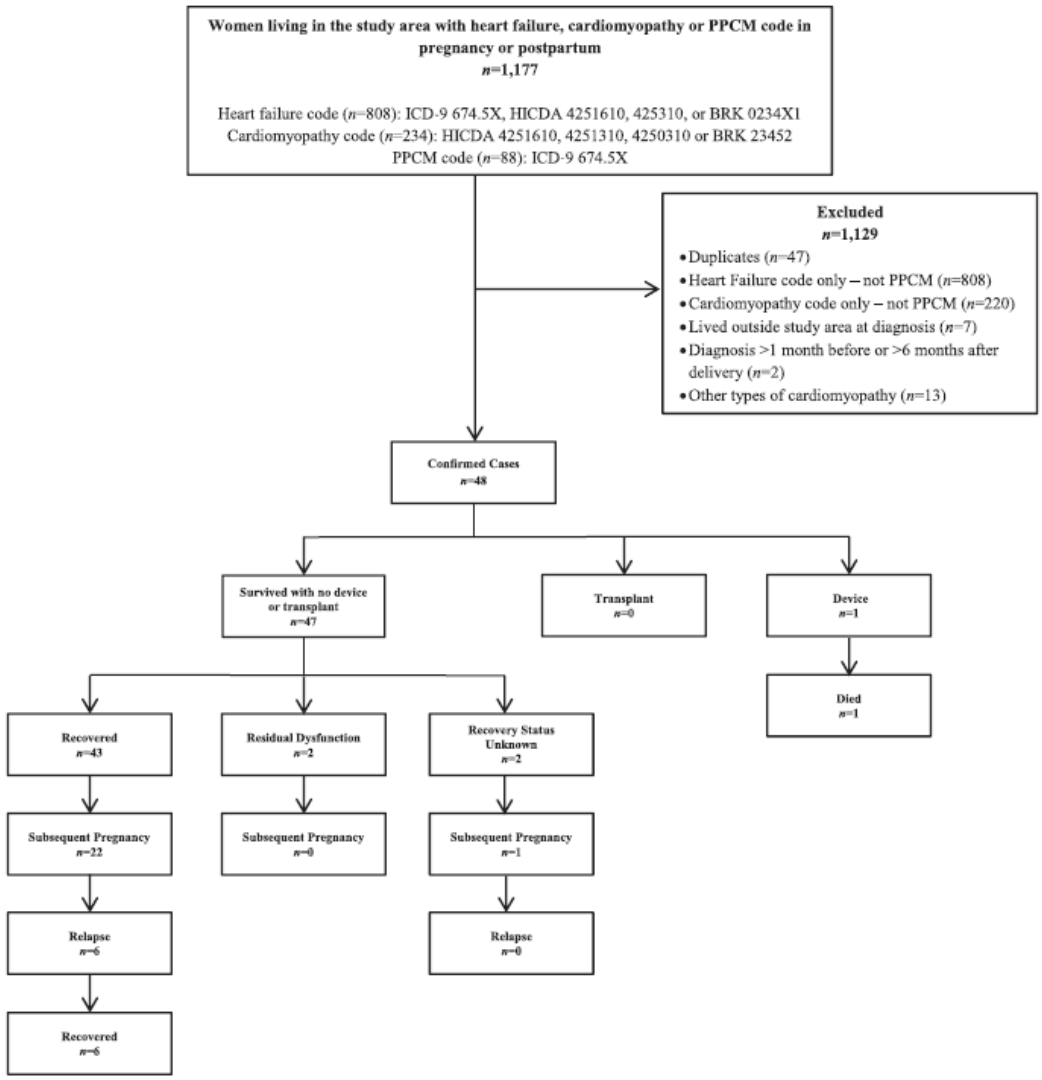

Fig. 1. Patient cohort with outcomes. From an initial cohort of 1177 women, 48 cases of peripartum cardiomyopathy (PPCM) were confirmed. 47 out of 48 women survived. One woman received an intra-aortic balloon pump and subsequently died. There were no transplants in this cohort. 43 women recovered cardiac function (left ventricular ejection fraction of ≥50% on echocardiogram), 2 had residual left ventricular dysfunction, and 2 had no follow-up echocardiograms so the recovery status could not be determined, but both were functionally recovered. At least 22 of the recovered women had subsequent pregnancies, as well as 1 woman whose recovery status was unknown. One woman with unknown recovery status (functionally recovered) had 1 subsequent pregnancy and did not relapse symptomatically, but no echocardiogram was conducted. Six of the recovered cases relapsed (12.5% rate of relapse) with at least 1 pregnancy, but all 6 subsequently recovered after relapse.

medical records available through the REP and entered into a Research Electronic Data Capture (REDCap) database.[18]

Statistical Analysis

The incidence was calculated for all Olmsted County female residents who were 15–55 years of age and considered to be at risk for PPCM. Annual birth rates for Olmsted County residents were obtained from the Minnesota Health Statistics Annual Summary Reports.[19,20] To compare cases and controls, the Student's t test or Wilcoxen–Mann–Whitney test were used to assess differences for continuous variables with normal or skewed distribution, respectively. The Fisher exact test or the χ^2 test

were used to evaluate categorical variables. A P value of <.05 was considered statistically significant. Categorical data are presented as frequency (n) and percent (%) and numeric data as mean ± standard deviation for normally distributed data and median (interquartile range) for non-normally distributed data, unless otherwise specified. Missing data were excluded from the analyses. Column total percentages are based on excluding missing data. Data were analyzed using Stata/IC 15.[21]

Results

Fifteen women in the single county area of Olmsted County, Minnesota, who met the definition for a diagnosis of PPCM were identified. Based on vital statistics data from the Minnesota Department of Health,[19,20] the incidence of PPCM from 1970 through 2014 in Olmsted County, Minnesota, was determined to be 20.3 cases per 100,000 live births.

An additional 33 women who lived in the larger 27 county REP area and met the criteria for a diagnosis of PPCM were identified that, when added to the 15 cases from Olmsted County, provided the 48 overall number of cases for the case control study (Fig. 1).'Ninety-six women were identified as controls with a 2:1 matching based on age, race, and number of infants born during the index pregnancy. Demographics of cases and controls are listed in Table 1. The mean age of the cohort was 28 years (range 15−44 years) (Table 1). The cohort was 79.2% White, 18.7% Black (a mix of African American [6.2%] and African immigrants [12.5%]) and 1 woman (2.1%) who identified as both Native American and Hispanic. Women in the PPCM cohort had a higher median body mass index than women in the control cohort (25.2 kg/m^{2}vs 23.6 kg/m^2, P = .01), were more likely to be overweight or obese (66.7% vs 41.7%, P = .005), and were more likely to have government-sponsored health insurance (ie, Medicaid), whereas women in the control cohort were more likely to have private health insurance (53.3% vs 25.6%, P = .001) (Table 1). There were no statistically significant differences in marital status, education level, smoking status, and history of alcohol consumption or drug use between the 2 groups. The median length of follow-up was shorter for cases compared to controls (7.2 years vs 12.8 years, P < .001) (Table 1).

Comorbidities for the 2 groups are compared in Table 2. Women in the PPCM cohort were more likely to have a history of hypertension (8.3% vs 2.1%, P = .01), anxiety (25.0% vs 10.4%, P = .03) and migraine (43.8% vs 15.6%, P< .001) compared with controls (Table 2). There were no differences observed in hyperlipidemia, heart disease, cancer, depression, asthma, allergies, infections, diabetes, or chemical exposure between the 2 groups (Table 2). Among the women for whom these data were available, women diagnosed with PPCM were more likely to have a history of hypertensive disorders of pregnancy (HDP), predominantly gestational hypertension and preeclampsia (40.0% vs 4.2%, P = .02), and a higher likelihood of gestational diabetes (4.8% vs 3.1%, P = .04) in previous pregnancies (Table 3).

Table 1. Maternal Demographic Characteristics of Cases and Controls*

Patient Characteristics	Case (n = 48)	Control (n = 96)	P Value
Age (y)	28 ± 7.0	28 ± 7.0	—
Prepregnancy BMI (kg/m^2)	25.2 (20.5–36.6)	23.6 (21.6–28.0)	.01
BMI category			.005
<25.0	16 (33.3)	56 (58.3)	
≥25.0	32 (66.7)	40 (41.7)	
Race/ethnicity			—
White	38 (79.2)	76 (79.2)	
American Indian	1 (2.1)	2 (2.1)	
Black	9 (18.7)	18 (18.7)	
African American	3 (6.2)	7 (6.2)	
African Immigrant	6 (12.5)	11 (12.5)	
Hispanic	1 (2.1)	2 (2.1)	
Marital status			.07
Single	13 (27.1)	26 (27.1)	
Married	24 (50.0)	61 (63.5)	
Domestic partner	11 (22.9)	9 (6.4)	
Education			.84
<High school	6 (13.3)	13 (13.7)	
High school or GED	12 (26.7)	19 (20.0)	
Some college or associate degree	15 (33.3)	36 (37.9)	
≥College degree	12 (26.7)	27 (28.4)	
Health insurance			.001
Private	21 (46.7)	70 (74.4)	
Medical assistance/ Medicaid	24 (53.3)	24 (25.6)	
Smoking			.16
At diagnosis	15 (31.2)	16 (18.0)	
Before pregnancy	8 (16.7)	23 (25.8)	
Never	25 (52.1)	50 (56.2)	
Alcohol use			.44
At diagnosis	3 (6.5)	1 (1.6)	
Before pregnancy	24 (52.2)	37 (57.8)	
Never	19 (41.3)	26 (40.6)	
Drug use			.82
Current	3 (6.2)	3 (3.8)	
Past	7 (14.6)	11 (14.1)	
Never	38 (79.2)	64 (82.1)	
Length of follow-up† (y)	7.2 (4.1–12.6)	12.8 (8.2–18.8)	<.001

Data are number (%), mean ± standard deviation, or median (interquartile range) unless otherwise specified.
*Percentages are based on column totals excluding unknown data.
†Follow-up was defined as years of medical records available for review after the index pregnancy delivery.
Abbreviations: BMI, body mass index; GED, general educational development or general education diploma.

Index pregnancy characteristics are listed in Table 4. Women in the PPCM cohort were more likely to have been diagnosed with HDP (56.3% vs 12.5%, P < .001) and more likely to have been placed on bed rest (28.2% vs 12.6%, P = .03) during their index pregnancy compared with women in the control group. The index pregnancies of women diagnosed with PPCM were less likely to have been planned pregnancies than those of controls (32.4% vs 54.4%, P = .03). Women in the PPCM cohort were also significantly more likely to have had an emergency cesarean section than women in the control cohort (43.8% vs 14.6%, P < .001). Women in the PPCM cohort were more likely to have had a cardiac indication for cesarean section than women in the control cohort (55.1% vs 7.1%, P = .01)

Table 2. Medical History of Cases and Controls

Comorbidity	Case ($n=48$)	Control ($n=96$)	P Value
Hypertension	4 (8.3)	2 (2.1)	.01
Hyperlipidemia	1 (2.1)	6 (6.3)	.43
All heart disease*	3 (6.3)	7 (7.3)	.99
Arrhythmia	3 (6.3)	3 (3.1)	.39
Other heart disease†	0 (0.0)	4 (4.2)	.55
Cancer‡	2 (4.2)	2 (2.1)	.60
Any mental health diagnosis	26 (54.2)	35 (36.5)	.04
Depression	22 (45.8)	31 (32.3)	.14
Anxiety	12 (25.0)	10 (10.4)	.03
Other mental health diagnosis	15 (31.3)	18 (18.8)	.10
Asthma	11 (22.9)	18 (18.8)	.66
Allergies	23 (47.9)	33 (34.4)	.15
Infections	28 (58.3)	55 (57.3)	.91
Diabetes	0 (0.0)	2 (2.1)	.55
Migraine	21 (43.8)	15 (15.6)	<.001
Autoimmune disease§	0 (0.0)	5 (5.2)	.17
Chemical exposure¶	6 (12.5)	4 (4.2)	.08

Data are number (%).
Percentages are based on column totals excluding unknown data.
*Three cases with arrhythmia.
†Three controls with mitral valve prolapse, and 1 control with patent foramen ovale.
‡Two cases had malignant melanoma, both treated only with excision. One control had thyroid cancer treated with excision and iodine ablation and one control had laryngeal squamous cell carcinoma treated with excision. No cases or controls were treated with chemotherapy or chest radiation.
§One control with ulcerative colitis, one control with Graves' disease and 3 controls with Hashimoto's thyroiditis.
¶Two cases with black mold exposure, 2 cases with pesticide exposure, 2 cases with occupational exposure.

(Table 4). Infants born to women in the PPCM cohort had a lower median gestational age (37 weeks vs 39 weeks, $P=.004$), were significantly more likely to be born prematurely (< 37 weeks gestation) (43.8% vs 22.9%, $P=.003$),

Table 3. Obstetric History of Cases and Controls Before the Index Pregnancy*

Obstetric history	Case ($n=48$)	Control ($n=96$)	P Value
Parity			
Median parity†	1 (0 – 2.5)	1 (0 – 2.5)	.34
Nulliparous	28 (58.3)	43 (44.8)	.16
Primipara or multipara	20 (41.7)	53 (55.2)	.16
Primipara or multipara women	$n=20$	$n=53$	
Multifetal gestations	0 (0.0)	0 (0.0)	—
Hypertensive disorders of pregnancy‡	8 (40.0)	4 (4.2)	.02
Gestational diabetes§	1 (4.8)	3 (3.1)	.04

Data are number (%) or median (interquartile range) unless otherwise specified.
Percentages are based on column totals excluding unknown data.
*The index pregnancy is the pregnancy associated with initial peripartum cardiomyopathy diagnosis for cases and the matched pregnancy for controls.
†Parity ranged from 0 to 6 for cases and 0 to 5 for controls.
‡Hypertensive disorders of pregnancy includes gestational hypertension, preeclampsia, eclampsia, preeclampsia superimposed on chronic hypertension, and unspecified types. Six missing.
§Five missing.

Table 4. Index Pregnancy Characteristics of Cases and Controls*

Characteristics	Case ($n=48$)	Control ($n=96$)	P Value
Assisted reproduction	4 (8.3)	13 (13.5)	.42
Access to standard medical care during pregnancy	27 (75.0)	78 (82.1)	.36
Planned pregnancy	11 (32.4)	50 (54.4)	.03
Single parenting	10 (20.8)	21 (23.1)	.96
Hypertensive disorders of pregnancy	27 (56.3)	12 (12.5)	<.001
Gestational diabetes	2 (4.4)	9 (9.5)	.50
Antibiotic use during pregnancy	21 (70.0)	53 (56.4)	.19
Bed rest	11 (28.2)	12 (12.6)	.03
Tocolytic therapy	2 (4.3)	11 (11.6)	.22
Method of delivery			.001
Spontaneous vaginal	16 (33.3)	59 (61.5)	.001
Assisted vaginal	6 (12.5)	12 (12.5)	.99
Planned caesarean section	5 (10.4)	11 (11.5)	.85
Emergency caesarean section	21 (43.8)	14 (11.6)	<.001
Indication for caesarean section			
Cardiac	11 (55.4)	1 (7.1)	.01
Obstetric	10 (47.6)	13 (92.9)	
No. of neonates			
Single	40 (83.3)	80 (83.3)	—
Twins	7 (14.9)	14 (14.9)	
Triplets	1 (2.1)	2 (2.1)	
Neonate sex			0.68
Male	23 (41.8)	51 (45.1)	
Female	32 (58.2)	62 (54.9)	
Gestational age (wk)	37 (33–39)	39 (37–40)	.004
Premature (<37)	21 (43.8)	22 (22.9)	.003
Birthweight (g)	2445 (2012–3459)	3190 (2550–3562)	.01
Low birth weight (<2500)	22 (45.8)	28 (24.8)	.01
Breastfeeding			
Yes	22 (59.5)	69 (75.8)	.06
Breastfeeding in cases only			
After delivery	22 (59.5)	—	.009
Post diagnosis	9 (24.3)	—	

Data are number (%) or median (interquartile range) unless otherwise specified.
Percentages are based on column totals excluding unknown data.
*The index pregnancy is the pregnancy associated with initial peripartum cardiomyopathy diagnosis for cases and the matched pregnancy for controls.

had a significantly lower median birth weight (2445 g vs 3190 g, $P=.01$) and were more likely to be born at a low birth weight (<2500g) (45.8% vs 24.8%, $P=.01$). Women in the PPCM cohort seemed to be less likely to breastfeed, but this difference did not reach statistical significance (59.9% vs 75.8%, $P=.06$.) However, the rates of breastfeeding in the PPCM cohort decreased significantly after diagnosis (59.9% vs 24.3%, $P=.009$) (Table 4).

Table 5 presents characteristics, including physical examination at diagnosis, echocardiography findings, and treatments and outcomes for the 48 cases in our cohort. Eleven of the women (22.9%) were diagnosed with PPCM during pregnancy and the other 37 (77.1%) were diagnosed postpartum, with the median time of diagnosis being 4 days postpartum (Table 5). The majority of cases (41/48, 85.4%) presented with elevated blood pressure[22] and/or heart failure symptoms (44/48, 91.7%) with 1 patient missing information on symptoms at diagnosis. Indications for cardiac screening in the 3 cases without heart failure symptoms

Table 5. Disease Characteristics of Women Diagnosed With Peripartum Cardiomyopathy ($n = 48$)

Disease Characteristic	Value
Timing of diagnosis[*] (days)	4 (0–12)
During pregnancy	11
Postpartum	37
Clinical features	
Blood pressure	
Systolic (mm Hg)	140 (126 – 154)
Diastolic (mm Hg)	89 (79 – 104)
Elevated[†]	41 (85.4)
Heart rate (bpm)	103.5 (88 – 120)
Murmurs[‡]	14 (29)
Signs suggestive of left heart failure[§]	
Yes	36 (75.0)
Unknown	2 (4.2)
Signs suggestive of right heart failure[¶]	
Yes	33 (68.8)
Unknown	5 (10.4)
Echocardiograph parameters	
EF (%)	34 (24 – 40)
LVEDD (cm)	5.7 (5.1–6.0)
LVESD (cm)	4.5 (4.1–4.9)
Ventricular septal wall thickness (cm)	1.0 (0.9–1.1)
Posterior wall thickness (cm)	0.9 (0.9–1.1)
RV enlargement[‖]	9 (18.8)
RV hypokinesis[‖]	16 (33.3)
LA volume index (mL/m^2)	34 (27 – 38)
Valvular heart disease,[#,‖]	20 (41.7)
Pericardial effusion[‖]	20 (41.7)
Treatments	
Treatment with medication	47 (97.9)
ACE inhibitor	42 (87.5)
Angiotensin II receptor blocker	2 (4.2)
Beta blocker	38 (79.2)
Diuretic	42 (87.5)
Blood thinner	17 (35.4)
Bromocriptine	0 (0.0)
Vasodilator	10 (20.8)
Anti-arrhythmic	10 (20.8)
Calcium channel blocker	2 (4.2)
Nitroglycerin	3 (6.3)
Potassium	4 (8.3)
Magnesium sulfate	4 (8.3)
Mechanical circulatory support	0 (0.0)
Cardiac device implantation[**]	1 (2.1)
VAD	0 (0.0)
Outcomes	
Length of follow-up after diagnosis (y)	7.3 (4.1 – 12.2)
Transplant	0 (0.0)
Death	1 (2.1)
Left ventricular recovery[††,‡‡]	43 (89.6)
Persistent cardiac dysfunction[§§]	2 (4.2)

Data are number (%) or median (interquartile range) unless otherwise specified.

Percentages are based on column totals excluding unknown data.

[*]Diagnosis timing ranged from 2 days before delivery to 185 days (6 months) postpartum with 7 women diagnosed on the day of delivery.

[†]Elevated blood pressure as defined as a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg as in the 2020 International Society of Hypertension Global Hypertension Practice Guidelines.[22]

[‡]Seven missing.

[§]Rales, wheezing, pulmonary edema.

[¶]Jugular venous distension, ascites, peripheral edema.

[‖]Eight missing.

[#]Designation of valvular heart disease was based on echocardiogram interpretations and included disease categorized as mild/moderate, moderate, moderate/severe, or severe. Valvular disease was found in just the mitral valve in 11 patients and in just the tricuspid valve in 6 patients. An additional 2 patients had disease in both the mitral and tricuspid valves and 1 patient had disease in the mitral, tricuspid, and pulmonary valve.

[**]Intra-aortic balloon pump.

[††]Left ventricular recovery defined as a left ventricular ejection fraction of ≥50% by echocardiogram.

[‡‡]Recovery time ranged from 3 days to just >12 years with a median of 4.5 months. Two patients had residual dysfunction, 1 died, and 2 had no follow-up echocardiogram, so the official recovery status is not known, but both were functionally recovered.

[§§]Persistent cardiac dysfunction defined as a left ventricular ejection fraction of ≤50%.

Abbreviations: ACE, angiotensin-converting enzyme; bpm, beats per minute; EF, ejection fraction; LA, left atrial; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; RV, right ventricle; VAD, ventricular assist device.

included arrhythmias and a new heart murmur. The median LVEF at diagnosis was 34% (range 12%−45%) and the median LV end diastolic diameter was 5.7 cm (range 4.0−7.4 cm). Forty-seven of the women (97.9%) were treated with medications, the most common being angiotensin-converting enzyme inhibitors (87.5%, $n = 42$), diuretics (87.5%, $n = 42$), and beta-blockers (79.2%, $n = 38$) (Table 5). One patient had an intra-aortic balloon pump placed and subsequently died (Table 5, Fig. 1). This death was the only one in the cohort. No pacemakers or internal cardiac defibrillators were implanted and no patients underwent LV assist device implantation or transplantation during a median follow up time of 7.3 years (range 0.3−27.8 years) (Table 5, Fig. 1).

Supplementary Fig. 1 shows the trends in LVEF of the confirmed cases over the first 5 years of the study. Forty-three of the women (89.6%) diagnosed with PPCM recovered cardiac function (LVEF ≥ 50% per follow-up echocardiography) (Table 5, Fig. 1). The timing of the recovery ranged from 3 days to just >12 years, with the median time to recovery approximately 4.5 months (Table 5). Two women had residual cardiac dysfunction and no follow-up echocardiograms were recorded for 2 additional women in the PPCM cohort, so recovery status could not be determined (Fig. 1).

Among the control cohort of 96 women, 56 (62.6%) had a total of 105 subsequent pregnancies, resulting in 82 (78.1%) live births, 18 (17.1%) spontaneous abortions, and 5 (4.8%) terminations. Twenty-three of the 48 women (56.1%) diagnosed with PPCM had a total of 37 subsequent pregnancies resulting in 25 (67.6%) live births, 5 (13.5%) spontaneous abortions, and 7 (18.9%) terminations (Table 6). Pregnancy termination was significantly higher in cases compared with controls ($P = .01$) (Table 6). Among the women diagnosed with PPCM, 10 (30.3%) of the subsequent pregnancies were planned, 23 (65.2%) were unplanned, with information unavailable regarding planning for 6 pregnancies (Table 6). Twenty-two of the women (95.7%) recovered cardiac function (LVEF of ≥50% per follow-up echocardiography) before subsequent pregnancy. One woman had no follow-up echocardiograms after index pregnancy diagnosis, so recovery status at subsequent pregnancy was unknown (Fig. 1). Fifteen women (65.2%) were on cardiac medication during their subsequent pregnancies (Table 6). The relapse rate in the PPCM cohort was 12.5%

Table 6. Obstetric and Cardiac Outcomes of Subsequent Pregnancies of Cases and Controls

Outcomes	Cases ($n=48$)	Controls ($n=96$)	P Value
No. of women with subsequent pregnancies*	23 (56.1)	56 (62.6)	.46
Subsequent pregnancies†	($n=37$)	($n=105$)	
Planned	10 (30.3)	‡	—
Unplanned	23 (69.7)	‡	—
Pregnancy outcome			
Delivered	25 (67.6)	82 (78.1)	.20
Spontaneous abortion	5 (13.5)	18 (17.1)	.80
Terminated	7 (18.9)	5 (4.8)	.01
Women on cardiac medication	15 (65.2)	‡	—
Beta blocker§	14	‡	—
Calcium channel blocker	1	‡	—
Digoxin	1	‡	—
Maternal outcome			
Relapse¶	6 (12.5)	‡	—
On cardiac medication at time of relapse	4 (66.7)	‡	—
Recovery after relapse‖	6 (100.0)	‡	—
Sterilization	16 (33.3)	33 (34.4)	.90

Data are number (%) unless otherwise specified.
Percentages are based on column totals excluding unknown data.
*For 7 cases and 7 controls subsequent pregnancy status is unknown.
†For 4, subsequent status, no data are available regarding planning of pregnancy.
‡Data either not applicable or not obtained.
§One woman was treated with both a beta blocker and a calcium channel blocker.
¶Relapse defined as decrease in the left ventricular ejection fraction to ≤45%.
‖LV recovery defined as a left ventricular ejection fraction of ≥50% by echocardiogram.

($n=6$), but all 6 cases recovered normal LV function after their relapse (Table 6 and Fig. 1). Similar rates of women in each cohort underwent sterilization procedures after index delivery (33.3% vs 34.4%, $P=.90$).

Discussion

The estimate of the incidence of PPCM in Olmstead County, Minnesota from 1970 through 2014 was 20.3 cases per 100,000 live births, which is lower than previous estimates of 25 to 185 per 100,000 live births.[5–7,9,13,23] Fifteen cases were found in Olmsted County and an additional 33 cases for a total of 48 cases in the larger 27 county region. However, owing to the lower percentage coverage rate (61%) for the REP in the 27 county region, PPCM incidence for the larger region could not be calculated. From an initial 1177 patients identified using diagnosis codes for heart failure, cardiomyopathy and PPCM, only 48 (55%) of the 88 women with a diagnosis code for PPCM met the diagnostic criteria for PPCM after record review by a physician experienced with PPCM (Fig. 1).[1] The most common reasons for exclusion included a LVEF of >45% and a diagnosis of other types of cardiomyopathy (Fig. 1). Our study may reflect a more accurate population-level incidence than previously published studies, because all cases in this study were confirmed using medical record data, whereas previously published studies[5–7,9,13,23] relied on diagnosis codes and may have overestimated the disease incidence by including women who had the diagnosis code for PPCM in their medical record but did not meet the diagnostic criteria for PPCM.

The mean age at PPCM diagnosis in this study was 28 years (Table 1), with 62.5% of cases occurring in women ≤30 years in contrast with previous studies that found an association between PPCM diagnosis and advanced maternal age.[6,8,9,13] Previous studies reported that Black women have the highest rates of PPCM, followed by non-Hispanic White women, with Hispanics and Asians having the lowest rates.[5,6,9,13,23–25] Based on US Census data, the population within the study area was 90.2–97.4% non-Hispanic White and 1.3–3.7% Black during the study period, whereas cases in this cohort were 79.2% non-Hispanic White and 18.8% Black, supporting previous reports that PPCM cases seem to occur at a higher rate among Black women compared with non-Hispanic White women.[15]

Previous reports have also suggested an increased risk of PPCM with multiparty[5,8–12,25] and multifetal gestation.[26] In the current study, we did not observe an association between multiparity and PPCM diagnosis, as 28 of the 48 women (58.3%) with PPCM were nulliparous (Table 3). Similar to previous studies, however, multifetal gestation during the index pregnancy (17.0%, $n=8$ in cases) occurred at a higher rate in women diagnosed with PPCM compared with the national rates for multifetal gestation that ranged from 2.1% to 3.5% during the time period of this study.[27]

HDP have been associated with an increased risk of PPCM.[26,28,29] Twenty-seven of the cases (56.3%) in this study were diagnosed with HDP during their index pregnancy, a rate significantly higher than controls (12/96, 12.5%, $P \leq .001$) (Table 4). Preeclampsia was the most common HDP diagnosis among cases, occurring in 18 of the 48 women (37.5%) (data not shown), which is more than nine times the 4% preeclampsia rate among women in the United States.[30] This finding aligns with previous studies that have reported that preeclampsia is one of the strongest risk factors for PPCM.[26,31]

This study identified prior diagnoses of anxiety or migraine as novel possible risk factors for PPCM (Table 2). Anxiety may increase the risk of cardiovascular disease by increasing inflammation and inducing endothelial dysfunction, 2 factors that are postulated to play a role in the pathogenesis of PPCM.[32] Migraine may also be a risk factor for developing PPCM, although with a small sample size of incident cases, this may also simply reflect migraine as a common disease state in women. It is important to note, however, that migraine is a known risk factor for cardiovascular and cerebrovascular disease, potentially increasing risk through pathways including HDP.[33–35] Migraine, preeclampsia, and PPCM have all been associated with vascular dysfunction owing to hormone imbalances and angiogenic factors including vascular endothelial growth factor, soluble fms-like tyrosine kinase-1, estrogen, relaxin-2, prolactin, and placental growth factor.[33,36–41] Further

investigation, including determining whether or not migraine subtype (with or without aura, for example) is more predictive of PPCM and whether increased frequency of migraine during pregnancy or only postpartum heightens risk of PPCM, is warranted.

Similar to previous studies,[5,8,42,43] the findings from this study suggest that infants born to mothers with PPCM have an increased risk for adverse birth outcomes, including prematurity and low birthweight (<2500 g) compared with those born to mothers in the control cohort (Table 4). These adverse outcomes are important to note, because premature birth and low birth weight are both associated with increased infant mortality and a variety of developmental and medical issues for the child.[44]

Another important finding in this study is that the rate of breastfeeding in women with PPCM decreased significantly after diagnosis (Table 4). Women discontinued breastfeeding for a variety of reasons, including their perceived compromised physical or mental health, not having ready access to their infants while hospitalized, a lack of awareness by treating physicians about the safety of cardiac medications during lactation, and/or a concern that breastfeeding may be detrimental to the mother's recovery based on the proposed mechanistic link between PPCM and the nursing hormone prolactin.[37,45] The World Health Organization recommends exclusive breastfeeding for 6 months and continued breastfeeding for ≥1−2 years[46] because the lack of breastfeeding is associated with an increased risk of diabetes, ovarian and breast cancers, and postpartum depression in women and higher rates of mortality, infections, eczema, asthma, childhood obesity, diabetes, leukemia, and lower intelligence in children.[47,48] Mothers with PPCM and their physicians would likely benefit from increased education and awareness regarding which cardiac medications are safe to use during lactation and that breastfeeding seems to have no detrimental effect on outcomes among women with PPCM according to several published reports.[49−51] Further investigation into the short- and long-term outcomes of infants born to mothers diagnosed with PPCM is necessary so that appropriate counseling and care can be provided to mothers and infants.

Nearly 90% of the women with PPCM in this study recovered normal LV function with a median recovery time of 4.5 months (Table 5). It should be noted that approximately one-half of the women who had not recovered by year one did not have follow-up echocardiograms until 1−12 years after diagnosis, at which time they had recovered. Owing to the retrospective nature of the study, the precise timing of recovery was difficult to establish. However, our data suggest that cardiac function can continue to improve for many years after PPCM diagnosis. Guideline-directed recommendations for follow-up assessment of women diagnosed with PPCM would likely enhance our understanding regarding degree and timing of LV recovery in patients.

In our study, 5 of 43 woman (11.6%) with PPCM who recovered LV function suffered a decline in cardiac function, between 6 months to 9.3 years after recovery, unrelated to a subsequent pregnancy (data not shown). One woman suffered cardiac toxicity from medications taken for an unrelated condition and recovered. A second woman recovered by one year and then had 2 occasions with deterioration in cardiac function despite remaining on cardiac medications throughout that time period with her most recent echocardiogram demonstrating a LVEF of ≥50%. Three women had discontinued all cardiac medications after recovery but then suffered declines in cardiac function at 3.5, 6.0, and 9.3 years after recovery. All 3 women recovered cardiac function after cardiac medications were restarted. Most medical experts agree that guideline-directed medical therapy for heart failure should be continued indefinitely in women with PPCM who have persistent cardiac dysfunction. However, there is no clear consensus on how to treat women with PPCM with recovered LV function.[2,52] Data regarding the long-term risk of cardiac deterioration if medications are stopped is conflicting.[53,54] Two recent studies suggest that women with LV recovery may still have LV diastolic dysfunction, decreased exercise capacity, ongoing angiogenic imbalance, and residual myocardial injury.[55,56] Noting that 5 women in our PPCM cohort experienced decline in LV function after recovery unrelated to subsequent pregnancy highlights the difficulty in determining the duration of medical treatment after recovery and the importance of long-term regular cardiac follow-up for women diagnosed with PPCM, including those with recovered cardiac function.

Many women with PPCM desire to have additional pregnancies after diagnosis. Decisions regarding subsequent pregnancy are challenging, because all women with PPCM are at risk for a decrease in LV function and possibly even death. Experts agree that women with persistent significant cardiac dysfunction are at greatest risk for cardiac complications during subsequent pregnancy and should be counseled against future pregnancy, while women with recovered cardiac function may consider subsequent pregnancy.[2,57,58] There are no proven risk factors for relapse during subsequent pregnancy among women with recovered LVEF, so careful monitoring during and after pregnancy is indicated. Although the sample size is small, our study results support the consensus that women diagnosed with PPCM with recovered cardiac function can have successful subsequent pregnancies (Table 6). Of note, 4 of the women in our study who relapsed during subsequent pregnancy were on cardiac medications at the time of relapse, highlighting that heart failure therapy does not guarantee freedom from relapse (Table 6). In addition, the large number of unplanned subsequent pregnancies and the higher rate of terminations in women diagnosed with PPCM indicate that contraceptive counseling on an ongoing basis, not simply shortly after PPCM diagnosis, is critical.

There are several limitations to this study. The small sample size prevented any subgroup analysis. The lack of racial/ethnic diversity in the REP compared with other regions of the United States may limit the generalizability of the study. Owing to the retrospective nature of the study, data are restricted to what is available in medical records and therefore the timing of subsequent echocardiograms varied between patients, adding uncertainty to calculations such as length of time to recovery. In addition, some cases

of PPCM may have been missed because the REP does not have complete coverage of medical records for all 27 counties. This factor prevented an incidence calculation for the entire study area. A major strength of our study, however, is the use of data from the REP, a well-established, high-quality, federally funded resource for epidemiologic research. In addition, the use of complete medical record review to confirm the diagnosis leading to a well-defined cohort of PPCM cases from a specific geographical area with long-term follow-up is particularly noteworthy. These strengths, as well as the almost complete capture rate of medical records for all residents of Olmsted County, Minnesota, made it possible to calculate a precise incidence estimate for that area.[14–16] These strengths, along with the verification of diagnosis by medical record review, minimized referral bias and misclassification, which are common in coding-based studies. This study was also strengthened by the range of data collected and analyzed, as well as the abundance of data in areas addressing knowledge gaps related to PPCM including long-term outcomes of mothers, infant outcomes, and outcomes of subsequent pregnancies.

Conclusions

The population-based incidence of PPCM was 20.3 cases per 100,000 live births in Olmsted County, Minnesota. Among the well-characterized cohort of women with PPCM in this study, a history of anxiety and a history of migraine emerged as novel risk factors. The majority of women recovered LV function days to years after diagnosis. A minority of women with recovered LV function experienced subsequent LVEF decline months to years after recovery. Infants of mothers with PPCM had an increased risk of prematurity and low birth weight. Finally, women with recovered LVEF before subsequent pregnancy experienced no long term decline in LVEF after pregnancy.

Disclosures

The authors declare no financial or other conflicts of interest. E.J.D. participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, L.T.C. participated in analysis and interpretation of the data and critically revising the article for important intellectual content, C.A.M participated in the acquisition, analysis, and interpretation of the data and revising the article critically for intellectual content, D.A.A. participated in the analysis, and interpretation of the data and revising the article critically for intellectual content, T. D.R. participated in analysis and interpretation of data and revising the article critically for important intellectual content, L.A.B. participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, and revising the article critically for important intellectual content, and D.F. participated in the conception and design of the study, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content. All authors read and approved the final version of the article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2020.12.021.

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CV

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EDUCATION

Doctor of Public (DrPH), Environmental Health and Engineering 2012-2021
Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
Honors: Health, Human Resources & Services Public Health Training Grant 2012-2013
Environmental Health Sciences Student Org. DrPH representative 2012-2014

Master of Public Health 2010-2011
Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
Certificate: The Risk Sciences and Public Policy
Capstone: Sex Differences in Vitamin D Binding Protein are Associated with Increased Myocarditis in Men and Male Mice.

Bachelor of Art, Major Biochemistry & Minor German 1999-2003
Occidental College - Los Angeles, California
Honors: Truman Scholarship (4 years)
Occidental College Tenure Track Neurobiologist Search Committee

WORK EXPERIENCE

Cardiovascular Research Liaison 2015-current
Mayo Clinic, Jacksonville, FL

- Appointment to the Division of Cardiovascular Diseases to help develop and facilitate a translational research program for the department.
- Developed and lead monthly Cardiovascular Research Conference for the department.
- Coordinated Fellows research experiences and projects.
- Assist in the development and implementation of human subjects research for the department including protocol development, IRB applications, study coordination, and funding proposals.
- Liaise with other units that support research – including the Clinical Trials Unit, Office of Special Projects Administration, Institutional Review Board, and Health Sciences Research.
- Liaise with outside vendors and organizations.

Research Trainee 2015
Mayo Clinic, Rochester, MN

- Appointment to the Division of Cardiovascular Diseases to conduct research on the incidence, risk factors, environmental associations, and outcomes of Peripartum Cardiomyopathy using the Rochester Epidemiology Project's database.

Research Assistant
Children and Nature Network, Minneapolis, MN 2014-2015

- Conducted comprehensive literature review on the effects of exposure to nature on children's physical health and created annotated bibliography of identified peer-reviewed studies.
- Produced written research summary synthesizing collected information and identifying gaps and future directions for research.

Teaching Assistant 2013-2013
Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

- **Food & Waterborne Disease -** contributed to writing of exams, interacted with students by email, in person, and in the classroom setting to enhance their learning experience, and administered and graded exams.
- **Professional Epidemiology Methods I** – co-taught lab sessions, conducted office hours regularly to assist students, interacted with students individually and in a class setting, graded class reports.

ASPH/EPA Environmental Health Fellow 8/2011-8/2012
Association of Schools of Public Health /US Environmental Protection Agency, Washington, D.C

- Co-Author on EPA report *America's Children and the Environment-Third Edition*, published January 2013.
- Collaborating with EPA researchers in Washington, Boston, and Research Triangle Park to develop web-based tools for community level cumulative risk assessment. Developing a model for including health outcomes in the Community-Focused Exposure and Risk Screening Tool (C-FERST) using Asthma as the health outcome. Helping to develop the modeling function of Community Cumulative Assessment Tool (CCAT) and working on a case study to apply the tool to a community for the first time. These tools and models will be used to assist communities in identifying, prioritizing, for community level health concerns.

Research Specialist 6/2011-9/2011
Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

- Conducted immunological research on the role of vitamin D and vitamin D binding protein in an animal model of autoimmune myocarditis.
- Developed standard operating procedures for the research group including for PCR, gel electrophoresis, and mouse genetic typing.
- Contributed to data analysis and manuscript writing.

Certified Clinical Research Coordinator - Cancer Institute 7/2007-6/2010
Benaroya Research Institute, Seattle, Washington

- Recruitment coordinator – screened medical records of every patient seen in the clinic daily to identify potential study participants and then present research studies to identified patients.
- Coordinate Genitourinary Oncology trials **-** Complete all aspects of clinical trials including study start up, recruitment, informed consent process, coordinate participant visits, meet with patients in a clinical setting, collect and manage data, and process and ship blood and tissue specimens.

Clinical Research Assistant - Type I Diabetes Institute 1/2007-7/2007
Benaroya Research Institute, Seattle, Washington

- Performed duties to support the conduction of clinical trials including managing a type I diabetes registry, conducting patient visits, acting as a phlebotomist, processing specimens, conducting outreach at health fairs and other events, and completing internal review board submissions.

Research Scientist – Immunology 6/2003-1/2007
University of Washington, Seattle, WA

- Executed directed research regarding the innate immune response to Pseudomonas aeruginosa including the development of transgenic mice expressing human genes.
- Conducted management duties including: general lab organization, chemical inventory, supply and equipment procurement, safety standards enforcement and waste management.
- Developed proficiency in animal and laboratory techniques including PCR, RTPCR, ELISA, LUMINEX, DNA and RNA isolation, flow cytometry, western blots, transgenics, bacterial cloning, and cell culture.

Teaching Assistant 2001-2003
Occidental College, Los Angeles, CA

- Prepared and instructed laboratory classes with the professors, graded examinations and laboratory reports, led review sessions, and peer-advised up to 50 students on course material for Organic Chemistry, Introduction to Molecular Biology, and Molecular Biology classes.

Research Intern - Summer Undergraduate Research Program 2001
University of Texas Medical Branch, Galveston, TX

- Conducted molecular research to enhance the understanding of how certain molecules work to protect proteins from damage during freezing or dehydration.
- Facilitated research collaboration between lab at UTMB and lab at Occidental College.

PROFESSIONAL DEVELOPMENT

Computer Skills:	Microsoft Office Products (Word, Excel, Access, and PowerPoint), STATA, ArcGIS Pro, REDCap
Languages:	English (fluent), German (fluent)
Memberships:	American Association of Immunologists (2016-2017) American Public Health Association (2011-2015) Organization for the Study of Sex Differences (2011-present) Sigma Xi - National Scientific Research Fraternity (2001-2013) Association of Clinical Research Personnel (2007-2011) Southwest Oncology Group (2007-2010)
Awards & Honors:	U.S. Public Health Service Training Grant, JHSPH & NIH (2012-2013) Certificate of Appreciation, Clinical Research Program, Benaroya Research Institute (2008) Truman Scholarship, Occidental College (1999-2003) Sealy Center for Structural Biology Award (2001) University of Texas Medical Branch Certificate of Merit (2001)

Selected Volunteer: Mayo Clinic Florida - American Heart Association Heart Walk Communications Chair (2015-2021)
Why Not Us Foundation – Project HERO (2014-2015)
Johns Hopkins Bloomberg School of Public Health Green Student Group (2010-2013)
JH-U-Turn (The Really Big Super Cheap Hopkins Garage Sale) (2011)
Johns Hopkins Bloomberg School of Public Health Career Fair Volunteer (2011)
Amara Parenting and Adoption Agency Board Intern (2005-2006)
Exceed Board of Directors Program (2005-2006)
Habitat for Humanity – Occidental College Chapter (2000-2003)

PUBLICATIONS

Peer-reviewed

Douglass EJ, Blauwet LA. (**2021**) Peripartum Cardiomyopathy. Cardiology Clinics, 2021-02-01; 39 (1): 119-142. doi: 10.1016/j.ccl.2020.09.008.

Douglass EJ, Cooper LT, Morales-Lara AC, Adedinsewo DA, Rozen TD, Blauwet LA, Fairweather D. (**2021**) A Case-Control Study of Peripartum Cardiomyopathy Using the Rochester Epidemiology Project. Journal of Cardiac Failure. 27 (2):132-142. doi: 10.1016/j.cardfail.2020.12.021.

Bruce AJ, Pincelli TP, Heckman MG, Desmond CM, Arthurs JR, Diehl NN, **Douglass EJ**, Bruce CJ, Shapiro SA. (**2020**) A Randomized, Controlled Pilot Trial Comparing Platelet-Rich Plasma to Topical Minoxidil Foam for Treatment of Androgenic Alopecia in Women. Dermatologic Surgery. 46(6):826–832. doi: 10.1097/DSS.0000000000002168.

Coronado MJ, Bruno KA, Blauwet LA, Tschöpe C, Cunningham MW, Pankuweit S, van Linthout S, Jeon ES, McNamara DM, Krejčí J, Bienertová-Vašků J, **Douglass EJ**, Abston ED, Bucek A, Frisancho JA, Greenaway MS, Hill AR, Schultheiss HP, Cooper LT Jr, Fairweather D. (**2019**) Elevated Sera sST2 Is Associated With Heart Failure in Men ≤50 Years Old With Myocarditis. J Am Heart Assoc. Jan 22;8(2): e008968. doi: 10.1161/JAHA.118.008968. PubMed PMID: 30638108; PubMed Central PMCID: PMC6497352.

Vuky J, Pham HT, Warren S, **Douglass E**, Badiozamani K, Madsen B, Hsi A, Song G. (2012) Phase II Study of Long-Term Androgen Suppression With Bevacizumab and Intensity-Modulated Radiation Therapy (IMRT) in High-Risk Prostate Cancer. Int J Radiat Oncol Biol Phys. Mar 15;82(4):e609-15. Epub 2011 Dec 28.

Krishnegowda G, Hajjar AM, Zhu J, **Douglass EJ**, Uematsu S, Akira S, Woods AS, Gowda DC. (2005) Induction of proinflammatory responses in macrophages by the glycosylphosphatidylinositols of Plasmodium falciparum: cell signaling receptors, glycosylphosphatidylinositol (GPI) structural requirement, and regulation of GPI activity. J Biol Chem. Mar 4; 280(9):8606-16.

Not peer reviewed

Axelrad D, Adams K, Chowdhury F, D'Amico L, **Douglass E**, Hudson G, Lam J, Lorenz A, McCoy E, Miller G, Newhouse K, Nweke O, Cantor Paster D, Sturza J, Underhill L, Weber K.

America's Children and the Environment, Third Edition. US Environmental Protection Agency. January 2013.

PUBLICATIONS UNDER REVIEW

Adedinsewo DA, Johnson PW, **Douglass EJ**, Attia, IZ, Phillips SD, Goswami RM, Yamani MH, Connolly HM, Rose CH, Sharpe EE, Blauwet LA, Lopez-Jimenez F, Friedman PA, Carter RE, Noseworthy PA. (2021) Detecting Cardiomyopathies in Pregnancy and the Postpartum Period with an Electrocardiogram-Based Deep Learning Model. JACC Submitted May 2021. Under Review

Krishnarao K*#, Bruno KA*, Di Florio DN, Hill AR, Cornell LF, Tan W, Geiger XJ, **Douglass EJ**, Fairweather D#, Yamani MH#. (2021) Endothelin 1 upregulation predicts chemotherapy-induced cardiotoxicity in patients with breast cancer. JACC. Submitted April 2021. Under Review* denotes co-first author, # denotes co-corresponding author.

ABSTRACTS

Bruno KA, Cooper LT, Mathews JE, **Douglass EJ**, Brandt JE, Bucek A, Coronado MJ, Fairweather D. Sex differences in the effect of vitamin D on inflammatory heart disease: protective in women but damaging in men Cardiology. 2017; 137:294.

Fairweather D, Bruno KA, Mathews JE, Coronado MJ, **Douglass EJ**, Hill AR, Frisancho JA, Bucek A, Blauwet LA, Cooper LT. Sex differences in biomarkers of heart failure Cardiology. 2017; 137:260.

Stafford K, Cooper L, **Douglass E**, Brandt J, Bucek A, Coronado M, Kew R, Fairweather D. Sex differences in the effect of vitamin D on inflammatory heart disease: protective in women but damaging in men. J Immunol. 2013 May 1; 190:43.1.

ORAL PRESENTATIONS

Douglass EJ, Fairweather D, Blauwet LA. A population level epidemiological study of peripartum cardiomyopathy in a27 county region surrounding Olmsted County, Minnesota. (2018) Presented at the International Congress of Cardiac Problems in Pregnancy, Bologna, Italy on February 23.

Douglass EJ, & Fairweather D. Sex Differences in Vitamin D Binding Protein are Associated with Increased Myocarditis in Men and Male Mice. (2011) Presented at Johns Hopkins Bloomberg School of Public Health, MPH Capstone Symposium on May 14.

POSTERS

Adedinsewo D, Siddiqui H, Attia Z, Cohen-Shelly M, **Douglass E**, Noseworthy P, Carter R. 2021. Title: Performance of a Deep Learning Model on Digitized Paper ECGs. Poster presented by Adedinsewo at 2021 Mayo Clinic AI Symposium held virtually May 17-18.

Bruno KA, **Douglass EA**, Salomon G, Jain A, Cooper LT, Coronado MJ, Kew RR, Fairweather D. 2020. Title: Vitamin D Binding Protein As A Potential Biomarker For Heart Failure In Myocarditis:

Translational Animal Model Reveals Mechanism. Poster presented by Bruno KA at the Heart Failure Society of America Annual Meeting held Virtually on September 30-October 6**.**

Whelan E*, Bruno KA, Coronado MJ, Blauwet LA, **Douglass EJ**, Abston ED, Bucek A, Frisancho JA, Greenaway MS, Hill AR, Cooper LT, Fairweather D. 2019. Title: Elevated sera sST2 predicts heart failure in men under the age of 50 with clinically suspected myocarditis. Poster presented by Whelan E at the University of North Florida Showcase of Osprey Advancements in Research and Scholarship held in Jacksonville, FL on April 3.

Bruno KA, Mathews JE, Greyer HD, Molina FA, Hill AR, DiFlorio DN, Scott AJ, Yang AL, Cooper LT, Hoyne JB, **Douglass EJ**, Brandt JE, Bucek A, Coronado MJ, Fairweather D. 2018. Title: Translational studies of sex differences in vitamin D/ vitamin D receptor on myocarditis. Poster presented by Bruno KA at the Celebration of Women's Health Research held in Rochester, MN on October 18.

Bruno KA, Mathews JE, **Douglass EJ**, Hill AR, Cooper LT, Hoyne JB, Fairweather D. 2018. Title: Sex differences in Vitamin D alter inflammation during heart disease. Poster presented by Bruno KA at the American Heart Association: Basic Cardiovascular Sciences Scientific Sessions (BCVS) held in San Antonio, TX on July 30-August 2.

Bruno KA, Coronado MJ, Blauwet LA, **Douglass EJ**, Abston ED, Bucek A, Frisancho JA, Greenaway MS, Hill AR, Cooper LT, Fairweather D. 2018. Title: Elevated sera sST2 predicts heart failure in men under the age of 50 with clinically suspected myocarditis. Poster presented by Bruno KA at the Florida Chapter of the American Academy of Cardiology Annual Meeting held in Orlando, FL on August 17-19

Di Florio DN*, **Douglass EJ**, Bruno KA, Hill AR, Mathews JE, Haley WE, Fairweather D. 2018. Title: Sex differences in vitamin D and urinary stone diseases. Poster presented by Bruno KA at the National Kidney Foundation held in Austin, TX on April 10-14.

Sousou JM*, Bruno KA, DiFlorio DN, Hill AR, Mathews JE, Morales C, **Douglass EJ**, Rahinduwage H, Petrikovics I, Hoyne JB, Cooper LT, Fairweather D. 2018. Title: Vitamin D deficient diet decreases cardiac function during myocarditis in females, Poster presentation at Organization for the Study of Sex Differences Annual Meeting held in Atlanta, GA on April 30-May 3.

Mease AA*, Bruno KA, Di Florio DN, **Douglass EJ**, Haley WE, Fairweather D. 2018. Title: Cardiac involvement in urinary stone disease: sex differences in vitamin D, Poster presented by Mease AA at the Organization for the Study of Sex Differences Annual Meeting held in Atlanta, GA on April 30-May 3.

Di Florio DN*, **Douglass EJ**, Bruno KA, Hill AR, Mathews JE, Haley WE, Fairweather D. 2018. Sex Differences in Vitamin D and Urinary Stone Diseases. Poster presented by Di Florio DN at the Association for Clinical and Translational Science annual meeting in Washington, D.C on March 6-9.

Douglass E, Fairweather D, Blauwet L. A 2017. Title: population level epidemiological study of peripartum cardiomyopathy in Olmsted County, Minnesota. Poster presented at the Celebration of Women's Health at Mayo Clinic in Rochester, Minnesota on October 18.

Bruno KA, Mathews JE, Greyer HD, Molina FA, Hill AR, DiFlorio DN, Scott AJ, Yang AL, Cooper LT, Hoyne JB, **Douglass EJ**, Brandt JE, Bucek A, Coronado MJ, Fairweather D. 2017. Title: Translational studies of sex differences in vitamin D/ vitamin D receptor on myocarditis. Presented by Bruno KA, at the Celebration of Women's Health at Mayo Clinic in Rochester, Minnesota on October 18.

Stafford K, Cooper L, **Douglass E**, Brandt J, Bucek A, Coronado M, Kew R, Fairweather D. 2013. Title: Vitamin D receptor signaling reduces inflammation in female mice with myocarditis, but increases inflammation in males: implications for translation studies, Poster presented by Stafford K at Organization for the Study of Sex Differences held in Weehawken, NY on April 25-27.

Stafford K, Molina F, Clifford M, **Douglass E**, Cooper L, Brandt J, Bucek A, Fairweather D. 2013. Title: Vitamin D receptor signaling reduces inflammation in female mice with myocarditis, but increases inflammation in males: implications for translation studies, Poster presented by Stafford K at Society for Women's Health Research held in Washington, DC on July 19.

Stafford K, Cooper L, **Douglass E,** Brandt J, Bucek A, Coronado M, Kew R, Fairweather D. 2013. Title: Sex differences in the effect of vitamin D on inflammatory heart disease: protective in women but damaging in men, Poster presented by Stafford K at American Association of Immunologists held in Honolulu, Hawaii on May 3 - 7.

Stafford K, **Douglass E**, Cooper L, Bucek A, Coronado M, Brandt J, Fairweather D. 2013. Title: Vitamin D receptor signaling reduces inflammation in female mice with myocarditis, but increases inflammation in males: implications for translation studies. Poster presented by Stafford K at Heart Failure Society of America held in Orlando, FL on September 22-25.

Erika J. Douglass, Michael J. Coronado, Adriana Bucek, Douglas W. Mahoney, Jo D. Carryer, Leslie T. Cooper Jr, and DeLisa Fairweather. 2012. Title: Sex Differences in Vitamin D Binding Protein are Associated with Increased Myocarditis in Men and Male Mice. Poster presented at the 8th International Congress on Autoimmunity in Granada, Spain May.

Erika J. Douglass, Michael J. Coronado, Adriana Bucek, Douglas W. Mahoney, Jo D. Carryer, Leslie T. Cooper Jr, and DeLisa Fairweather. 2012. Title: Sex Differences in Vitamin D Binding Protein are Associated with Increased Myocarditis in Men and Male Mice. Presented at the Organization for the Study of Sex Differences 6th Annual Meeting in Baltimore. MD June 7-9.

Stafford K, Cooper L, **Douglass E**, Brandt J, Bucek A, Coronado M, Kew R, Fairweather D. 2012. Title: Sex differences in the effect of vitamin D on inflammatory heart disease: protective in women but damaging in men. Poster presented by Stafford K at Organization for the Study of Sex Differences held in Baltimore, MD on June 7-9.

Katlyn A Stafford, **Erika J. Douglass**, Jessica E. Brandt, Adriana Bucek, Michael J. Coronado, Richard R. Kew, Leslie T. Cooper Jr., and DeLisa Fairweather. Vitamin D receptor increases coxsackievirus B3 myocarditis. Poster presented by Stafford K at the Organization for the Study of Sex Differences 6th Annual Meeting in Baltimore. MD June 7-9.

Axelrad D, Adams K, Chowdhury F, D'Amico L, **Douglass E**, Hudson G, Lam J, Lorenz A, McCoy E, Miller G, Newhouse K, Nweke O, Cantor Paster D, Sturza J, Underhill L, Weber K. 2011. Title: Children's environmental health in the United States: Indicators from *America's Children and the Environment*. Poster presented by Axelrad DA at the American Public Health Association 139th Annual Meeting in Washington, DC.

Douglass E, Auton M, and Bolen DW. 2001. How Does Glycerol Enable Organisms to Survive Environmental Stress? Poster presented at 2001 Summer Annual Research Program Poster Session, University of Texas Medical Branch, Galveston TX, August.